IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBSTITUTE PETITION UNDER 37 C.F.R. §1.47 FOR FILING AN APPLICATION FOR PATENT WHEN A JOINT INVENTOR CANNOT BE REACHED

Dear Sir:

This is a Substitute Petition to accept a substitute Declaration For Patent Application (hereinafter "DECLARATION") pursuant to 37 C.F.R. §1.47(a), when an inventor refuses to sign or cannot be located or reached. This Substitute Petition replaces the Petition filed November 30, 2006. The Substitute Petition is necessitated by the receipt of an executed DECLARATION by inventor Charlott L.F. Deckhut (hereinafter "Deckhut"). At the time of filing the original Petition, inventor Deckhut did not return the executed DECLARATION. Because the inventor was not responsive by the time of filing the original Petition, it was concluded that inventor Deckhut was refusing to sign the substitute DECLARATION. On December 6, 2006, inventor Deckhut returned the executed substitute DECLARATION. This substitute Petition amends the original Petition by removing the section in the Statement of Facts by Frank J. Miskiel detailing the facts related to inventor Deckhut not responding to our requests. This Petition also provides the executed DECLARATION of inventor Deckhut.

Attorney Docket No. 18202-018001/1082
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number EV 740126578 US
Date of Deposit: **December 22, 2006**
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop Petition, Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Frank J. Miskiel

Frank J. Miskiel

REMARKS

The Commissioner is authorized to charge any fees that may be due in connection with this paper or with this application to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition.

The above-identified application lists eleven joint inventors. All eleven joint inventors executed a DECLARATION in connection with the filing of this application. The original DECLARATION, date-stamped by the Office on May 15, 2002, is attached as Exhibit A. On the original DECLARATION, Inventor Thomas R. Caferro ("Caferro") lined through the address on the printed DECLARATION and printed his then-current address, but inadvertently did not initial and date the changes on the DECLARATION. This was brought to Applicant's attention in the Notice of Allowance. A substitute DECLARATION is required to correct this defect.

A Petition to accept a substitute Declaration For Patent Application (hereinafter "DECLARATION") pursuant to 37 C.F.R. §1.47(a), when an inventor refuses to sign or cannot be located or reached, was filed in the above-captioned application on November 30, 2006, in connection with the payment of the Issue Fee in response to a Notice of Allowance. Since the filing of the original Petition, an inventor who had not responded to our request to return an executed DECLARATION has returned the executed DECLARATION. Therefore, this substitute Petition replaces the original Petition, providing a copy of the DECLARATION executed by inventor Charlott L.F. Deckhut.

Accompanying this Petition are:

(1) a copy of the originally executed and filed DECLARATION (EXHIBIT A);
(2) a copy of the Notice of Allowance, mailed August 31, 2006 (EXHIBIT B);
(3) a copy of the executed substitute DECLARATIONS from each of inventors Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Neelakandha S. Mani, Jyun-Hung Chen, Mark E. Adams and Charlott L.F. Deckhut (EXHIBIT C);
(4) a STATEMENT OF FACTS by Frank J. Miskiel, an associate of the undersigned attorney involved with prosecuting this application, with accompanying Exhibits (EXHIBIT D);
(5) a STATEMENT OF FACTS by Teresa Salazar-Fischer, a U.S. paralegal employed with the undersigned, with accompanying Exhibits (EXHIBIT E); and
(6) a return postcard.

Applicant hereby petitions pursuant to 37 C.F.R. §1.47(a) for acceptance of the substitute DECLARATION of the above-captioned application by other than all the inventors. A copy of the executed substitute DECLARATION is attached hereto.

Under 37 C.F.R. §1.47(a), if a joint inventor refuses to join in an application for patent or cannot be found or reached after diligent effort, the application may be made by the other inventor[s]. The above-captioned application names as inventors, Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Anthony W. Thompson, Thomas R. Caferro, Neelakandha S. Mani, Jyun-Hung Chen, Marquis L. Cummings, James P. Edwards, Mark E. Adams and Charlotte L.F. Deckhut. While diligent attempts have been made to obtain the signatures on the substitute DECLARATION of all of the joint inventors, despite diligent and repeated efforts, it has not been possible to locate and/or obtain the signatures of all of the inventors. Seven of the eleven joint inventors have executed the substitute DECLARATION. Of the four joint inventors who have not executed the substitute DECLARATION, Marquis L. Cummings ("Cummings") and James P. Edwards ("Edwards") have not responded to requests to sign the DECLARATION, and Thomas Caferro ("Caferro") and Anthony W. Thompson ("Thompson") could not be located. Also, provided as part of this Petition are a Statement of Frank J. Miskiel and a Statement of Teresa Salazar-Fischer documenting the efforts to obtain all of the signatures.

As described and documented in the attached Statements and Exhibits, diligent efforts were made to locate and/or contact inventors Cummings, Edwards, Caferro and Thompson. Despite these efforts, neither the undersigned nor the Assignee has been able to locate and/or contact joint inventors Cummings, Edwards, Caferro and Thompson. Therefore, inventors Cummings, Edwards, Caferro and Thompson cannot be found or reached after diligent effort.

Accordingly, in light of these efforts, and provision of the executed substitute DECLARATION of the other joint inventors (see EXHIBIT C), the fee set forth in 37 C.F.R. §1.17(g), and the last known address of each of the non-signing inventors Cummings, Edwards, Caferro and Thompson, favorable review of this Petition and Exhibits, and acceptance of the substitute DECLARATION in the above-captioned application without signature of joint inventors/applicants Cummings, Edwards, Caferro and Thompson, are respectfully requested.

* * *

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney's Docket No.: 18202-018001 / 1082

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Lin Zhi *et al.*	Art Unit	:	1623
Serial No.	:	10/080,503	Examiner	:	Lawrence E. Crane, Ph.D.
Conf. No.	:	8671	Customer No.	:	20985
Filed	:	February 22, 2002			
Title	:	**TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**			

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT A – a copy of the originally executed and filed DECLARATION.

DECLARATION

Utility Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS** the specification of which

(Check One)

☐ is attached hereto OR

☒ was filed on February 22, 2002 as United States Application Serial No. 10/080,503; PCT International Application No. and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Date of Filing	Priority Claimed Yes	No

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below.

Application Number(s)	Filing Date
60/271,115	February 23, 2001

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT international application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date	Status-Patented, Pending or Abandoned

Residence, post office address, citizenship and signature of inventor(s) set forth beginning on next page.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name Robert	MIDDLE Initial I.	LAST Name Higuchi	
	RESIDENCE & CITIZENSHIP	City Solana Beach	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	434 Marview Drive	City San Diego	State or Country California	Zip Code 92075

INVENTOR'S SIGNATURE ______ DATE 4/12/02

202	FULL NAME OF INVENTOR	FIRST Name Lin	MIDDLE Initial	LAST Name Zhi	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship People's Republic of China	
	POST OFFICE ADDRESS	3988 Via Cangrejo ~~7704 Roan Road~~ LZ	City San Diego	State or Country California	Zip Code 921~~29~~ 30 LZ

INVENTOR'S SIGNATURE ______ DATE 4/17/02

203	FULL NAME OF INVENTOR	FIRST Name Donald	MIDDLE Initial S.	LAST Name Karanewsky	
	RESIDENCE & CITIZENSHIP	City Escondido	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	1797 Continental	City Escondido	State or Country California	Zip Code 92029

INVENTOR'S SIGNATURE ______ DATE 4/18/02

204	FULL NAME OF INVENTOR	FIRST Name Anthony	MIDDLE Initial W.	LAST Name Thompson	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	4179 THIRD AVENUE ~~1733 Reed Avenue #4~~ APT 211 AWT	City San Diego	State or Country California	Zip Code ~~92109~~ 92103 AWT

INVENTOR'S SIGNATURE ______ DATE 4-18-02

SIGNED IN COUNTERPARTS

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name Thomas	MIDDLE Initial R.	LAST Name Caferro	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	17537 Matinal Road	City San Diego	State or Country California	Zip Code 92127

INVENTOR'S SIGNATURE ______________________ DATE ____________

202	FULL NAME OF INVENTOR	FIRST Name Neelakandha	MIDDLE Initial S.	LAST Name Mani	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship India	
	POST OFFICE ADDRESS	13109 Russet Leaf Lane	City San Diego	State or Country California	Zip Code 92129

INVENTOR'S SIGNATURE [signature] DATE 04/11/02

203	FULL NAME OF INVENTOR	FIRST Name Jyun-Hung	MIDDLE Initial	LAST Name Chen	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship Taiwan	
	POST OFFICE ADDRESS	7614 Palmilla Drive #58	City San Diego	State or Country California	Zip Code 92122

INVENTOR'S SIGNATURE Jyun-Hung Chen DATE 04/15/02

204	FULL NAME OF INVENTOR	FIRST Name Marquis	MIDDLE Initial L.	LAST Name Cummings	
	RESIDENCE & CITIZENSHIP	City Encinitas	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	917 Bracero Road	City Encinitas	State or Country California	Zip Code 92024

INVENTOR'S SIGNATURE [signature] DATE 4/18/02

SIGNED IN COUNTERPARTS

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name Thomas	MIDDLE Initial R.	LAST Name Caferro	
	RESIDENCE & CITIZENSHIP	City ~~San Diego~~ Holly Springs	State or Foreign Country ~~California~~ North Carolina	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	~~17537 Matinal Road~~ 101 Thornton Green Pl.	City ~~San Diego~~ Holly Springs	State or Country ~~California~~ NC	Zip Code ~~92127~~ 27540

INVENTOR'S SIGNATURE ______________ DATE 5/10/02

202	FULL NAME OF INVENTOR	FIRST Name Neelakandha	MIDDLE Initial S.	LAST Name Mani	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship India	
	POST OFFICE ADDRESS	13109 Russet Leaf Lane	City San Diego	State or Country California	Zip Code 92129

INVENTOR'S SIGNATURE ______________ DATE ______

203	FULL NAME OF INVENTOR	FIRST Name Jyun-Hung	MIDDLE Initial	LAST Name Chen	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship Taiwan	
	POST OFFICE ADDRESS	7614 Palmilla Drive #58	City San Diego	State or Country California	Zip Code 92122

INVENTOR'S SIGNATURE ______________ DATE ______

204	FULL NAME OF INVENTOR	FIRST Name Marquis	MIDDLE Initial L.	LAST Name Cummings	
	RESIDENCE & CITIZENSHIP	City Encinitas	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	917 Bracero Road	City Encinitas	State or Country California	Zip Code 92024

INVENTOR'S SIGNATURE ______________ DATE ______

SIGNED IN COUNTERPARTS

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name James	MIDDLE Initial P.	LAST Name Edwards	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	8723 Hesby Court	City San Diego	State or Country California	Zip Code 92129

INVENTOR'S SIGNATURE James P. Edwards DATE 09APR02

202	FULL NAME OF INVENTOR	FIRST Name Mark	MIDDLE Initial E.	LAST Name Adams	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	3512 Seahorn Circle	City San Diego	State or Country California	Zip Code 92130

INVENTOR'S SIGNATURE ______________________ DATE __________

203	FULL NAME OF INVENTOR	FIRST Name Charlotte	MIDDLE Initial L.F.	LAST Name Deckhut	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	3105 Kalmia Street	City San Diego	State or Country California	Zip Code 92104

INVENTOR'S SIGNATURE ______________________ DATE __________

204	FULL NAME OF INVENTOR	FIRST Name	MIDDLE Initial	LAST Name	
	RESIDENCE & CITIZENSHIP	City	State or Foreign Country	Country of Citizenship	
	POST OFFICE ADDRESS		City	State or Country	Zip Code

INVENTOR'S SIGNATURE ______________________ DATE __________

SIGNED IN COUNTERPARTS

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18, United States Code, § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

201	FULL NAME OF INVENTOR	FIRST Name James	MIDDLE Initial P.	LAST Name Edwards	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	8723 Hesby Court	City San Diego	State or Country California	Zip Code 92129

INVENTOR'S SIGNATURE ______________________ DATE __________

202	FULL NAME OF INVENTOR	FIRST Name Mark	MIDDLE Initial E.	LAST Name Adams	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	3512 Seahorn Circle	City San Diego	State or Country California	Zip Code 92130

INVENTOR'S SIGNATURE Mark E. Adams DATE 4/19/02

203	FULL NAME OF INVENTOR	FIRST Name Charlotte	MIDDLE Initial L.F.	LAST Name Deckhut	
	RESIDENCE & CITIZENSHIP	City San Diego	State or Foreign Country California	Country of Citizenship U.S.A.	
	POST OFFICE ADDRESS	3105 Kalmia Street	City San Diego	State or Country California	Zip Code 92104

INVENTOR'S SIGNATURE CDT DATE 4/10/02

204	FULL NAME OF INVENTOR	FIRST Name	MIDDLE Initial	LAST Name	
	RESIDENCE & CITIZENSHIP	City	State or Foreign Country	Country of Citizenship	
	POST OFFICE ADDRESS		City	State or Country	Zip Code

INVENTOR'S SIGNATURE ______________________ DATE __________

SIGNED IN COUNTERPARTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT B - a copy of the Notice of Allowance, dated August 31, 2006.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

20985 7590 08/31/2006

FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/31/2006

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,503	02/22/2002	Robert I. Higuchi	015110.0058.UTL1	8671

TITLE OF INVENTION: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$0	$1700	11/30/2006

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status above is to be removed, check box 5b on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check box 5a on Part B - Fee(s) Transmittal and pay the PUBLICATION FEE (if required) and 1/2 the ISSUE FEE shown above.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 07/06) Approved for use through 04/30/2007.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

20985 7590 08/31/2006

FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,503	02/22/2002	Robert I. Higuchi	015110.0058.UTL1	8671

TITLE OF INVENTION: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

APPLN. TYPE	SMALL ENTITY	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1400	$300	$0	$1700	11/30/2006

EXAMINER	ART UNIT	CLASS-SUBCLASS
CRANE, LAWRENCE E	1623	514-314000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
   - ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
   - ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
   (1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
   (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
   1 ____________
   2 ____________
   3 ____________

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies ____________

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number ____________ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)
- ☐ a. Applicant claims SMALL ENTITY status. See 37 CFR 1.27.
- ☐ b. Applicant is no longer claiming SMALL ENTITY status. See 37 CFR 1.27(g)(2).

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature ____________ Date ____________

Typed or printed name ____________ Registration No. ____________

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

UNITED STATES PATENT AND TRADEMARK OFFICE

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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,503	02/22/2002	Robert I. Higuchi	015110.0058.UTL1	8671

20985 7590 08/31/2006

FISH & RICHARDSON, PC
P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
CRANE, LAWRENCE E	
ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 08/31/2006

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 190 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 190 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 07/06) Approved for use through 04/30/2007.

Notice of Allowability	Application No. 10/080,503	Applicant(s) HIGUCHI ET AL.
	Examiner L. E. Crane	Art Unit 1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *the amendment filed May 19, 2006*.

2. ☒ The allowed claim(s) is/are *1-31,37-40,46,49-51,56-72,76,77 and 108*.

3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. ______ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: ______.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☒ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
   1) ☐ hereto or 2) ☐ to Paper No./Mail Date ______.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ______.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date 4/5/05(update)
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *08232006* .
7. ☒ Examiner's Amendment/Comment
8. ☐ Examiner's Statement of Reasons for Allowance
9. ☒ Other *PTO-1449 of 02/01/2005*

L. E. Crane, Ph.D., Esq.
Primary Patent Examiner
Technology Center 1600

Applicant is respectfully requested to supply an amended declaration because the handwritten alterations to the oath by inventor Caferro were not properly initialed and dated.

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. §1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

In claim **46**, the term "claim **45**" was amended to read
-- claim **1** --.

In claim **56** at line 108, the term -- and -- was added at the end of the line.

In claim **56** at line 111, the term "a pharmaceutically acceptable salt" was amended to read -- pharmaceutically acceptable salts --.

In claim **57** at line 25, the term -- and -- was added at the end of the line.

In claim **57** at line 28, the term "a pharmaceutically acceptable salt" was amended to read -- pharmaceutically acceptable salts --.

In claim **58** at line 67, the entire line was deleted in favor of the term -- m is 1; --.

Claim **75** was cancelled.

In claim **108** at line 4, the term "and o" was amended to read
-- and --.

Authorization for this Examiner's Amendment was given in a telephone interview with Frank Miskiel on August 21, 2006

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

All Post-Allowance Correspondence concerning this application must be mailed to:

BOX ISSUE FEE
COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

OR you can FAX them to the Office of Patent Publications at 571-273-8300, in order to expedite the handling of such correspondence as amendments under 37 C.F.R. §1.312; Information Disclosure Statements (IDS's), and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at **571-272-4200**. The Notice of Allowance also has an insert containing contact information for other items, including Issue Fees, receipt of formal drawings, and the status of the application.

LECrane:lec
08/23/2006

L. E. Crane, Ph.D. Esq.
Primary Patent Examiner
Technology Center 1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

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P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT C - a copy of the substitute DECLARATION executed by inventors Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Neelakandha S. Mani, Jyun-Hung Chen, Mark E. Adams and Charlotte L.F. Deckhut.

DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled

TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

( ) is attached hereto.
(X) was filed by an authorized person on my behalf on February 22, 2002 as Application Serial No. 10/080,503
(X) was amended on January 31, 2005, November 3, 2005, May 19, 2006, and by Examiner's amendment of July 11, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

Number	Country	Day/Month/Year Filed	Priority Claimed (Yes or No)
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
60/271,115	February 23, 2001

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
N/A		

PCT Application No.	Filing Date	Status
N/A		

We hereby declare that all statements made therein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Full name of joint inventor: Robert I. Higuchi

Inventor's signature: Robert I. Higuchi

Date: 11/3/06

Residence: 434 Marview Drive
San Diego, CA 92075

Citizenship: U.S.A

Full name of joint inventor: Lin Zhi

Inventor's signature: [illegible]

Date: 10/26/06

Residence: 3988 Via Cangrejo
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: Donald S. Karanewsky

Date: 01 Nov 2006

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ______________________

Date: ______________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ______________________

Date: ______________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ______________________

Date: ______________________

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: ______________________

Date: ______________________

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ______________________

Date: ______________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ______________________

Date: ______________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ______________________

Date: 11/1/06

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Jyun-Hung Chen

Inventor's signature: Jyun-Hung Chen

Date: Oct. 26, 2006

Residence: 7614 Palmilla Drive, #58
San Diego, CA 92122

Citizenship: Taiwan

Full name of joint inventor: Marquis L. Cummings

Inventor's signature: ________________

Date: ________________

Residence: 917 Bracero Road
Encinitas, CA 92024

Citizenship: U.S.A.

Full name of joint inventor: James P. Edwards

Inventor's signature: ________________

Date: ________________

Residence: 8723 Hesby Court
San Diego, CA 92129

Citizenship: U.S.A.

Full name of joint inventor: Mark E. Adams

Inventor's signature: Mark Adams

Date: ea 11/28/06

Residence: 12638 Carmel Country Road, #130
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Charlotte L.F. Deckhut

Inventor's signature:

Date: 11/28/06

Residence: 3105 Kalmia Street
San Diego, CA 92104

Citizenship: U.S.A.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
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ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT D – STATEMENT OF FACTS by Frank J. Miskiel.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.:	20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

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Alexandria, VA 22313-1450

STATEMENT OF FACTS BY FRANK J. MISKIEL IN SUPPORT OF A PETITION UNDER 37 C.F.R. §1.47 FOR FILING AN APPLICATION FOR PATENT WHEN A JOINT INVENTOR CANNOT BE REACHED OR LOCATED OR REFUSES TO SIGN

Dear Sir:

I am an attorney involved with the prosecution of the above-captioned application. Under my direction, a substitute Declaration For Patent Application (hereinafter "DECLARATION") was prepared and mailed by Teresa Salazar-Fischer, a paralegal employed with the undersigned at the firm. The DECLARATION was sent, on October 23, 2006, to Ms. Michele P. Travis, our contact paralegal employed by Ligand Pharmaceuticals, Inc., the Assignee of the above-captioned patent application, in order to obtain inventor signatures. The DECLARATION was provided with copies of the application and amendments made during prosecution of the application, to the above listed inventors. Michele P. Travis informed me that inventors Thomas R. Caferro (hereinafter "Caferro"), Anthony W. Thompson (hereinafter "Thompson"), Marquis L. Cummings (hereinafter "Cummings") and James P. Edwards (hereinafter "Edwards") are no longer employed by Ligand Pharmaceuticals, and that Ligand Pharmaceuticals has been attempting, but has not been able to contact or locate Caferro, Thompson, Cummings and Edwards. I also was unsuccessful in previous attempts to locate inventors Caferro and Thompson in connection with another matter.

On October 23, 2006, I instructed Ms. Salazar-Fischer to prepare copies of the substitute DECLARATION, the application and the amendments made during prosecution of the application and to send these documents via U.S. Certified Mail, Return Receipt Requested to each of inventors Caferro, Thompson, Cummings and Edwards using the addresses we had on file. Copies of the original specification, amendments made during prosecution and the substitute DECLARATION, which were mailed to each inventor, are provided as Exhibits 2-5.

Caferro

The last known mailing address for inventor Caferro is:

Thomas R. Caferro
101 Thorton Green Place
Holly Springs, NC 27540

On or around November 13, 2006, the package sent to inventor Caferro was returned in its original envelope to our office. The package was stamped "undeliverable as addressed, return to sender" and included the three-letter acronym "UTF" handwritten on the package. A copy of the stamped envelope from the package mailed to Caferro is provided as Exhibit 7. The acronym "UTF" is used by the Post Office to indicate "Unable to Forward," as evidenced by the entry for "UTF" in "The Free Dictionary by Farlex," available on-line at http://acronyms.thefreedictionary.com/utf. A copy of the definition for "UTF" is provided as Exhibit F.

On November 27, 2006 I contacted Ms. Travis, of Ligand Pharmaceuticals, Inc. and requested phone numbers for inventor Caferro. I was informed that there were no phone numbers in their inventor database for inventor Caferro. On November 27, 2006, I performed electronic searches on the Internet to locate inventor Caferro. I used the search engines provided by FreeKnowX.com and ZabaSearch.com to locate an address or phone number for inventor Caferro.

The FreeKnowX search engine provided an address for inventor Caferro. The address provided by the search engine is identical to the last known mailing address for inventor Caferro. No phone number was provided. The search engine for ZabaSearch returned an address and a phone number for inventor Caferro. The address provided by the search engine is identical to the last known mailing address for inventor Caferro. I called the number provided nine times at various times during the day and evening, and the phone was never answered. I also searched the North Carolina Voter Database and obtained information that suggests that inventor Caferro is actively living in Holly Springs, NC, but no contact information was available. Copies of the results of the searches are provided as Exhibit G.

As evidenced above, I have not been able to locate a current address for inventor Caferro nor have I been able to contact inventor Caferro by telephone. Accordingly, in light of these efforts, I conclude that inventor Caferro cannot be located or reached in connection with executing the substitute DECLARATION.

Thompson

The last known mailing address for inventor Thompson is:

Anthony W. Thompson
4179 Third Avenue, Apt. 211
San Diego, CA 92103

On or around November 13, 2006, the package sent to inventor Thompson was returned in its original envelope to our office. The package was returned stamped "undeliverable as addressed, return to sender" and included the three-letter acronym "FOE" handwritten on the package. A copy of the stamped envelope from the package mailed to Thompson is provided as Exhibit 8. The acronym "FOE" is used by the Post Office to indicate "Forwarding Order Expired," as evidenced by the entry for "FOE" in "The Free Dictionary by Farlex," available on-line at http://acronyms.thefreedictionary.com/foe. A copy of the definition for "FOE" is provided as Exhibit H.

On November 27, 2006 I contacted Ms. Travis, of Ligand Pharmaceuticals, Inc. and requested a phone number for inventor Thompson. I was informed that there was no phone number in their inventor database for inventor Thompson. On November 27, 2006, I performed electronic searches on the Internet to locate inventor Thompson. I used the search engines provided by FreeKnowX.com and ZabaSearch.com to locate an address or phone number for inventor Thompson.

The FreeKnowX search engine provided no information for inventor Thompson. The search engine for ZabaSearch provided seventeen listings for "Anthony W. Thompson," only one of which was an address in San Diego, CA. I called the number provided for the San Diego address and that number is no longer is service. Copies of the results of the searches are provided as Exhibit I.

As evidenced above, I have not been able to locate a current address for inventor Thompson nor have I been able to contact inventor Thompson by telephone. Accordingly, in light of these efforts, I conclude that inventor Thompson cannot be located or reached in connection with executing the substitute DECLARATION.

Cummings

The last known mailing address for inventor Cummings is:

Marquis L. Cummings
917 Bracero Road
Encinitas, CA 92024

On or around November 15, 2006, the Return Receipt postcard from the package sent to inventor Cummings was returned to our office. The package was delivered to the last

known mailing address for inventor Cummings. The postcard was signed by "Leeanna Cummings." Thus, the package was not signed by inventor Cummings. A copy of the postcard is provided as Exhibit 6.

By November 27, 2006, inventor Cummings had not returned an executed substitute DECLARATION. On November 27, 2006 I contacted Ms. Travis, of Ligand Pharmaceuticals, Inc. and requested a phone number for inventor Cummings. I was informed that there was no phone number in their inventor database for inventor Cummings. On November 27, 2006, I performed electronic searches on the Internet to locate inventor Cummings. I used the search engines provided by FreeKnowX.com and ZabaSearch.com to locate an address or phone number for inventor Cummings.

The FreeKnowX search engine provided no information for inventor Cummings. The search engine for ZabaSearch provided four listings for "Marquis L. Cummings," none of which was an address in San Diego, CA. No phone numbers were provided. Copies of the results of the searches are provided as Exhibit J.

As evidenced above, I have not been able to contact inventor Cummings by telephone. Although I have evidence that the package addressed to inventor Cummings was delivered to the last known mailing address, as evidenced by the signature on the returned Certified Mail Return Receipt postcard by someone with the same last name as inventor Cummings, I have not received an executed substitute DECLARATION from inventor Cummings. I conclude that, either the package delivered to the last known address was never delivered to inventor Cummings, or in the alternative, based on the conduct of inventor Cummings, since an executed substitute DECLARATION was not received from inventor Cummings, that inventor Cummings refuses to sign the substitute DECLARATION.

Edwards

The last known mailing address for inventor Edwards is:

James P. Edwards
8723 Hesby Court
San Diego, CA 92129

On or around November 6, 2006, the Return Receipt postcard from the package sent to inventor Edwards was returned to our office. The package was delivered to the last known mailing address for inventor Edwards. The postcard was signed by "Jackie Edwards." The package was not signed for by inventor Edwards. A copy of the postcard is provided as Exhibit 9.

By November 27, 2006, inventor Edwards had not returned an executed substitute DECLARATION. On November 27, 2006, I contacted Ms. Travis, of Ligand Pharmaceuticals,

Inc. and requested a phone number for inventor Edwards. I was informed that there was no phone number in their inventor database for inventor Edwards. On November 27, 2006, I performed electronic searches on the Internet to locate inventor Edwards. I used the search engines provided by FreeKnowX.com and ZabaSearch.com to locate an address or phone number for inventor Edwards.

The FreeKnowX search engine provided no information for inventor Edwards. The search engine for ZabaSearch provided fourteen listings for "James P. Edwards," one of which was an address that matched the last known mailing address. Copies of the results of the searches are provided as Exhibit K. I called the number provided and left messages on the answering machine, but no one at that phone number has returned my calls.

As evidenced above, I have not been able to contact inventor Edwards by telephone. Although I have evidence that the package addressed to inventor Edwards was delivered to the last known mailing address, as evidenced by the signature on the returned Certified Mail Return Receipt postcard by someone with the same last name as inventor Edwards, I have not received an executed substitute DECLARATION from inventor Edwards. I conclude that, either the package delivered to the last known address was never delivered to inventor Edwards, or in the alternative, based on the conduct of inventor Edwards, since an executed substitute DECLARATION was not received from inventor Edwards, that inventor Edwards refuses to sign the substitute DECLARATION.

Executed Substitute Declaration

On November 29, 2006, a letter from paralegal Michele P. Travis (on behalf of the Applicant) enclosing a substitute DECLARATION executed by joint inventors Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Neelakandha S. Mani, Jyun-Hung Chen and Mark E. Adams was received via Federal Express. On December 6, 2006, a letter from paralegal Michele P. Travis (on behalf of the Applicant) enclosing a substitute DECLARATION executed by joint inventor Deckhut was received via Federal Express (see Exhibit C).

Conclusion

In summary, in view of all of the actions taken as described above and documented in the attached Exhibits, it is believed that diligent efforts were made to locate and/or contact inventors Cummings, Edwards, Caferro and Thompson. Despite these efforts, I have not been able to locate and/or contact joint inventors Cummings, Edwards, Caferro and Thompson. Therefore, inventors Cummings, Edwards, Caferro and Thompson cannot be found or contacted after diligent effort.

Accordingly, in light of these efforts, and the provision of the executed substitute DECLARATION of the other joint inventors (see EXHIBIT C), the fee set forth in 37 C.F.R. §1.17(g), and the last known address of each of the non-signing inventors Cummings, Edwards, Caferro and Thompson, favorable review of this Petition and acceptance of the substitute DECLARATION in the above-captioned application without signature of joint inventors Cummings, Edwards, Caferro and Thompson, are respectfully requested.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

* * *

Respectfully submitted,

Frank J Miskiel

Frank J. Miskiel
Reg. No. 53,332

22 December 2006
Date

Attorney Docket No. 18202-018001 / 1082
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
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ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT E – STATEMENT OF FACTS by Teresa Salazar-Fischer.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
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P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF TERESA SALAZAR-FISCHER

I, TERESA SALAZAR-FISCHER, declare as follows:

1. I have been employed by Fish & Richardson P.C. since July 19, 2005. During the time in question I was the U.S. Patent Paralegal assigned to the above-captioned application.

2. On October 23, 2006, I was instructed by Frank J. Miskiel, an associate working on the above-captioned matter, to prepare a substitute DECLARATION for execution by the inventors (see Exhibit 1). A copy of the substitute DECLARATION, application as filed, and amendments made during prosecution were forwarded to paralegal Michele P. Travis, acting on behalf of Ligand Pharmaceuticals, Inc. (herein after "Applicant").

3. On October 30, 2006, I was instructed by Frank J. Miskiel to send a copy of the application as filed, copies of the amendments made during prosecution and the substitute DECLARATION, to each of Marquis L. Cummings (hereinafter "Cummings"), James P. Edwards (hereinafter "Edwards"), Thomas Caferro (hereinafter "Caferro") and Anthony W. Thompson (hereinafter "Thompson"), using the address for each that we had on file, via U.S. Certified Mail, Return Receipt Requested service.

4. On October 30, 2006, I mailed by U.S. Certified Mail a copy of the application as filed, copies of the amendments and the substitute DECLARATION to each of inventors Cummings, Edwards, Caferro and Thompson (see Exhibits 2 - 5).

5. On or around November 6, 2006, the Return Receipt Postcard from the package sent to inventor Edwards was returned. The package was signed for by Jackie Edwards (see Exhibit 6).

6. On or around November 13, 2006, the packages sent to inventors Caferro and Thompson were returned to our office marked "undeliverable as addressed, return to sender" by the U.S. Postal Service (see Exhibit 7 and Exhibit 8).

7. On or around November 15, 2006, the Return Receipt Postcard from the package sent to inventor Cummings was returned. The package was signed for by Leeanna Cummings (see Exhibit 9).

8. On November 29, 2006, a letter was received via Federal Express from paralegal Michele P. Travis (on behalf of the Applicant) enclosing a substitute DECLARATION executed by joint inventors Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Neelakandha S. Mani, Jyun-Hung Chen and Mark E. Adams (see Exhibit 10).

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

Respectfully submitted,

Date: 11/29/06

T. E. Salazar-Fischer

TERESA SALAZAR-FISCHER

Attorney Docket No. 18202-018001 / 1082
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT F – print-out of http://acronyms.thefreedictionary.com/utf webpage evidencing the definition of the acronym "UTF" from "The Free Dictionary by Farlex."

THEFREEDICTIONARY BY FARLEX

440,597,952 people served.

TheFreeDictionary Google

Unable to Forward (post office) Search ?

Word / Article Starts with Ends with Text

Dictionary/ thesaurus	Computing dictionary	Medical dictionary	Legal dictionary	Financial dictionary	Acronyms	Idioms	Columbia encyclopedia	Wikipe encycl

UTF

0.03 sec.

(redirected from *Unable to Forward (post office)*)

Page tools ?

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Feedback

Acronym	Definition
UTF	UCS Transformation Format
UTF	Udvidet Teknisk Forberedelseseksamen (Danish)
UTF	Unable to Forward (post office)
UTF	Underground Test Facility
UTF	Unicode Transformation Format (16 bit Unicode to 7/8 bit character conversion)
UTF	Unified Test System
UTF	Uniform Tight Frame
UTF	Unit Test Fixture
UTF	Universal Taekwon Do Federation
UTF	Universal Test Fixture
UTF	Use The Force
UTF	Utilization Training Facility

submit new definition

Acronyms browser ?

- UN/NA
- UN/SPSC
- UNA
- UNA-USA
- UNAA
- UNAAF
- UNAB
- **Unable to Forward (post office)**

Full browser ?

- unabashedly
- unabated
- unabatedly
- Unaberrated Focused Light Beam
- Unabhängige Arbeiterpartei (Independent
- Unable to Approve Departure for the Time Specified
- Unable to Reach
- Unable to

UNAC
UNACASTD
UNACE
UNACLA
UNADD
UNADDR
UNADJ

Workers Party)
- Unabhangige Arbeiterpartei Deutschlands
- Unabhängige Arbeiterpartei Deutschlands
- Unabhängige Verbreitung Christlicher Medien (German)
- Unabhängige Wählergemeinschaft (German: independent voter community)
- Unabhängiger Verwaltungssenat (Austria)
- Unability
- Unabkömmlich (German: Exempt from Military Service)
- unable
- Unable to Approve
- Unable to Approve Altitude Requested
- Unable to Approve Arrival for the Time Specified
- Unable to Approve Route Requested
- Unable to Assess
- Unable to Break in on Transmission (radiotelegraphy)
- Unable to Comply (ITU-T)
- Unable to Contact
- Unable to Establish Contact
- Unable to Forward
- **Unable to Forward (post office)**
- unable to hear think
- unable to help
- Unable To Locate
- Unable to Locate Complainant (Alabama Public Safety Radio Code)
- Unable to Maintain
- Unable to Monitor
- Unable to Obtain
- Unable to Perform (functional capacity evaluations/assessments)

Reproduce
- Unable To Reproduce Fault On Ground
- Unabled
- Unableness
- Unabomb
- Unabomber
- Unabomber (album)
- Unabomber (disambiguation)
- unabridged
- unabridged dictionary
- Unabsorbable
- Unabsorbed Depreciation (accounting/finance)
- Unabsorbed Loss Before Depreciation (accounting/finance)
- unabused
- UNAC

◉ TheFreeDictionary ○ Google

THEFREEDICTIONARY BY FARLEX | Unable to Forward (post office) | Search | ?

◉ Word / Article ○ Starts with ○ Ends with ○ Text

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
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P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT G – print-out of the search results returned from the FreeKnowX and ZabaSearch search engines for inventor Caferro and the results returned from the North Carolina Voter Database.

THE FREE DICTIONARY BY FARLEX

440,598,272 people served.

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foe Search ?

Word / Article Starts with Ends with Text

Dictionary/ thesaurus | Computing dictionary | Medical dictionary | Legal dictionary | Financial dictionary | Acronyms | Idioms | Columbia encyclopedia | Wikipedia encycl

FOE

Also found in: Dictionary/thesaurus, Columbia, Wikipedia, Hutchinson 0.03 sec.

Page tools ?
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Cite / link
Email
Feedback
Get a t-shirt of "FOE"

Acronym	Definition
FOE	Fact of Employment
FOE	Faculty of Education
FOE	Faculty of Engineering
FOE	Fat Opposite the Ribeye
FOE	Fiber Optics Equipment
FOE	Field/Follow-On Operational Evaluation
FOE	Final Operational Evaluation
FOE	Fleet of Eden (RPG)
FOE	Focus of Expansion (optics)
FOE	Follow-On Element
FOE	Follow-On Equipment
FOE	Follow-On Evaluation
FOE	Foreign Object Elimination (Northrop-Grumman and Boeing assembly line usage)
FOE	Forsvarets Etterretningstjeneste (Norwegian military intelligence agency)
FOE	Forwarding Order Expired
FOE	Fraternal Order of Eagles
FOE	Freakin' Operator Error (polite version)
FOE	Friends of English (English Conversation Club, South Korea)
FOE	Friends of Europe
FOE	Friends Of the Earth
FOE	Topeka, KS, USA - Forbes Field (Airport Code)

submit new definition

Acronyms browser ?

FODLS

Full browser ?

Fodors
FODP
Foederati

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT H – print-out of http://acronyms.thefreedictionary.com/foe webpage evidencing the definition of the acronym "FOE" from "The Free Dictionary by Farlex."

Information within reach

SEARCHING >> NAME: **Thomas Caferro** | CITY: **Holly Springs** | STATE: **NC**

MATCH: **1** INDIVIDUAL

1. CAFERRO THOMAS R & KRISTA
101 THORNTON GREEN PL
HOLLY SPRINGS NC 27540-8472
(000) 000-0000

Assets Check

Background Check

People Finder

Find more information on this person using these tools.

> LOCATE: INI

Name: T

Address:

City: H

State: N

Zip:

> LOCATE: BU

Name: T

Address:

Phone:

State: N

Phone Example: 1:

Business Find

Locate a Busine
Finder to locate
companies or pı
specific telephoı
potential client,

Search by Phone Number Search by Social Security Number Compl

ZABASEARCH **Search Any Full Name:** Thomas Caferro

Public Information **Results Summary:** 1 THOMAS CAFERRO / 2 T CAFERRO / 3 CAFERRO L

THOMAS CAFERRO - Background Check, 20 Year History Pren

www.Intelius.com Comprehensive Report. Criminal Records. Latest Contact Information.

Find THOMAS CAFERRO Pren

www.Intelius.com Get Current Phone and Address

THOMAS CAFERRO - 1 Listing

Leave a message for Thomas Caferro Check messages E-mail This Page ZabaAlert

Check messages for: Caferro - Thomas - Thomas Caferro Check YouTube

THOMAS R CAFERRO **Born Feb 1970** More Information on THOMAS R CAFERRO

101 THORNTON GREEN PL Map It Recorded: 11/16/2004 THOMAS R CAFERRO business listings

HOLLY SPRINGS, NC 27540 County **(919) 577-0043** Leave a message for THOMAS R CAFERRO

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T CAFERRO - 2 Listings

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THOMAS R CAFERRO **Born Feb 1970** More Information on THOMAS R CAFERRO

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CAFERRO - 3 Listings

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KRISTA K CAFERRO **Born May 1971** More Information on KRISTA K CAFERRO

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THOMAS R CAFERRO **Born Feb 1970** More Information on THOMAS R CAFERRO

101 THORNTON GREEN PL Map It Recorded: 11/16/2004 THOMAS R CAFERRO business listings

HOLLY SPRINGS, NC 27540 County **(919) 577-0043** Leave a message for THOMAS R CAFERRO

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TOM R CAFERRO **Born Feb 1970** More Information on TOM R CAFERRO

101 THORNTON GREEN PL Map It Recorded: 04/15/2001 TOM R CAFERRO business listings

HOLLY SPRINGS, NC 27540 County Leave a message for TOM R CAFERRO

www.ZabaSearch.com/Google - Background Check

Can't find THOMAS CAFERRO? Pren

TRY THIS DATABASE

Background Check on THOMAS CAFERRO Pren

www.PeopleLookUp.com 20 Year History

Search by Phone Number Search by Social Security Number **Complete Ba**

Search Any Full Name: Thomas Caferro

ZABASEARCH **being described as "Google on steroids." -**

Check for Messages Yellow Pages 30,000+ Free Databases Top 25 Searches Your Cu

Voter Data Results From The NC Statewide Database

Click Here to Search for Another Voter.

Name:	CAFERRO, THOMAS R
Voter Reg Num:	000031078246
County Name:	WAKE
Status:	ACTIVE
City:	HOLLY SPRINGS NC 27540
Race:	WHITE
Ethnicity:	NOT HISPANIC or NOT LATINO
Gender:	Male
Party:	UNAFFILIATED
Polling Place:	HOLLY SPRINGS TOWN HALL Click here to view images of your Polling Place
Address:	128 MAIN ST
City:	HOLLY SPRINGS, NC 27540
Polling Place:	Click Here for a Map of Your Polling Place
Voting Districts:	Click Here to View Your Voting Districts
Voter History:	Click Here to View Your Voter History

For more information regarding your voting jurisdictions, polling place location, or other vote information; please contact your county board of elections.

Results From The NC Statewide Database

Click Here to Search for Another Voter.

County	Status	Full Name (Total Found: 1)	City/State/Zip
WAKE	ACTIVE	CAFERRO, THOMAS R	HOLLY SPRINGS NC 2754C

For more information regarding your voting jurisdictions, polling place location, or other vote
information; please contact your county board of elections.
There are people currently on this search engine.
You logged onto this search engine at

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
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P.O. Box 1450
Alexandria, VA 22313-1450

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EXHIBIT I – print-out of the search results returned from the FreeKnowX and ZabaSearch search engines for inventor Thompson.

KnowX KnowX Standard KnowX Professional Superior RapSheets

Home | How it Works | Pricing | Contact Us | Site Map

Open an Account

STANDARD Login

USER NAME

PASSWORD

go

Forgot Login Info? click here

The Ultimate People Finder

Searching: Name: **Anthony W Thompson** | City: **San Diego** | State: **CA** | Zip: **92103**

0 Matches Found

Try Address Verification - Updated Nightly.

NEW SEARCH MODIFY SEARCH

Example Record

NI

Try Know: Tracer se locate har individual determine associate: more.

No matches were found.

Search Again for Free Using These Tips:

- Search for individuals in the U.S. only.
- Check spelling
- Avoid full middle names (middle initial may be listed)
- Search head-of-the-household name where possible
- If searching for a female, try a first initial and last name
- Avoid abbreviations (Mil will not expand to find Miller, Milken, Milton, etc.)
- If unsure of the exact city name, just enter the state
- Enter complete 5-digit zip code (partial number will not work)
- For more tips, go to our search tips

First Name: Anthony

Last Name: Thompson

City: San Diego

State: California

Zip: 92103 Search

Related Searches

Find more info on Anthony W Thompson by researching:

- Business Background Check
- Business Relationships
- Real Estate
- Reverse Address

Other Searches:

- Marriage Records
- Divorce Records
- Experian Reports
- Assets $
- Professional Licenses

Visit Partner Sites:

- Birth and Death Certificates

  Order certified birth, death, marriage, divorce certificates

Company Info | Public Records Info | Privacy Statement | Privacy at ChoicePoint | Legal

Search by Phone Number Search by Social Security Number C

ZABASEARCH **Search Any Full Name:** Anthony W Thompson

Public Information **Results Summary:** 8 A W THOMPSON / 13 ANTHONY THOMPSON / 17 ANT

A W THOMPSON - 8 Listings
Leave a message for Anthony W Thompson Check messages E-mail This Page ZabaAlert
Check messages for: Thompson - Anthony - Anthony W Thompson Check YouTube

More Information on A W THOMPSON
(619) 563-8942
www.ZabaSearch.com/Google -

More Information on ALDEN W THOMPSON
(858) 560-6870
www.ZabaSearch.com/Google -

More Information on ALDEN W THOMPSON
(858) 560-6870
www.ZabaSearch.com/Google -

Born Sep 1955 More Information on ANTHONY W THOMPSON

www.ZabaSearch.com/Google -

ANTHONY W THOMPSON **Born Sep 1975** More Information on ANTHONY W THOMPSON
1735 REED AVE Map It Recorded: 03/12/2002 ANTHONY W THOMPSON business listings
SAN DIEGO, CA 92109 County **(619) 272-5984** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ALVIN W THOMPSON More Information on ALVIN W THOMPSON
2992 G ST Map It Recorded: 10/05/2004 ALVIN W THOMPSON business listings
SAN DIEGO, CA 92102 County Leave a message for ALVIN W THOMPSON
www.ZabaSearch.com/Google - Background Check

ARTHUR W THOMPSON **Born 1928** More Information on ARTHUR W THOMPSON
4823 ARLENE ST Map It Recorded: 09/12/2003 ARTHUR W THOMPSON business listings
SAN DIEGO, CA 92117 County **(858) 576-2239** Leave a message for ARTHUR W THOMPSON
www.ZabaSearch.com/Google - Background Check

ALAN W THOMPSON **Born Aug 1962** More Information on ALAN W THOMPSON
7612 PALMILLA DR Map It Recorded: 04/15/2001 ALAN W THOMPSON business listings
SAN DIEGO, CA 92122 County Leave a message for ALAN W THOMPSON
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ANTHONY THOMPSON - 13 Listings
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ALAN W THOMPSON More Information on ANTHONY THOMPSON

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ALAN W THOMPSON Born Sep 1955 More Information on ANTHONY W THOMPSON
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ANTHONY THOMPSON Born 1979 More Information on ANTHONY THOMPSON
1459 ELDER AVE Map It Recorded: Unknown ANTHONY THOMPSON business listings
SAN DIEGO, CA 92154 County Leave a message for ANTHONY THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON Born 1979 More Information on ANTHONY THOMPSON
1459 ELDER AVE Map It Recorded: 06/23/2004 ANTHONY THOMPSON business listings
SAN DIEGO, CA 92154 County (619) 429-9387 Leave a message for ANTHONY THOMPSON
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ANTHONY W THOMPSON Born Sep 1975 More Information on ANTHONY W THOMPSON
1735 REED AVE Map It Recorded: 03/12/2002 ANTHONY W THOMPSON business listings
SAN DIEGO, CA 92109 County (619) 272-5984 Leave a message for ANTHONY W THOMPSON
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ANTHONY THOMPSON Born Apr 1948 More Information on ANTHONY THOMPSON
2006 PACIFIC MIST CT Map It Recorded: 04/04/2002 ANTHONY THOMPSON business listings
SAN DIEGO, CA 92139 County Leave a message for ANTHONY THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON More Information on ANTHONY THOMPSON
3010 DUMAS ST Map It Recorded: Unknown ANTHONY THOMPSON business listings
SAN DIEGO, CA 92106 County (619) 224-0539 Leave a message for ANTHONY THOMPSON
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ANTHONY R THOMPSON More Information on ANTHONY R THOMPSON
319 WILLIE JAMES JONES AVE Map It Recorded: 04/15/2001 ANTHONY R THOMPSON business listings
SAN DIEGO, CA 92102 County (619) 527-9912 Leave a message for ANTHONY R THOMPSON
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ANTHONY A THOMPSON More Information on ANTHONY A THOMPSON
4049 HOME AVE Map It Recorded: 04/15/2001 ANTHONY A THOMPSON business listings
SAN DIEGO, CA 92105 County Leave a message for ANTHONY A THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON More Information on ANTHONY THOMPSON
4110 UTAH ST Map It Recorded: 10/16/2003 ANTHONY THOMPSON business listings
SAN DIEGO, CA 92104 County Leave a message for ANTHONY THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON More Information on ANTHONY THOMPSON
5397 LA JOLLA MESA DR Map It Recorded: Unknown ANTHONY THOMPSON business listings
SAN DIEGO, CA 92109 County Leave a message for ANTHONY THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON More Information on ANTHONY THOMPSON
8386 CAPRICORN WAY Map It Recorded: Unknown ANTHONY THOMPSON business listings

SAN DIEGO, CA 92126 County Leave a message for ANTHONY THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY THOMPSON More Information on ANTHONY THOMPSON
8386 CAPRICORN WAY Map It Recorded: 07/01/2005 ANTHONY THOMPSON business listings
SAN DIEGO, CA 92126 County **(858) 695-6763** Leave a message for ANTHONY THOMPSON
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ANTHONY W THOMPSON - 17 Listings
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Check messages for: - - Anthony W Thompson Check YouTube

ANTHONY W THOMPSON Born 1940 More Information on ANTHONY W THOMPSON
2942 LINDEN AVE Map It Recorded: 05/21/2003 ANTHONY W THOMPSON business listings
BERKELEY, CA 94705 County **(510) 540-1937** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON Born 1940 More Information on ANTHONY W THOMPSON
2942 LINDEN AVE Map It Recorded: 05/21/2003 ANTHONY W THOMPSON business listings
BERKELEY, CA 94705 County **(510) 540-6538** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON Born 1947 More Information on ANTHONY W THOMPSON
81 RITZ COVE DR Map It Recorded: Unknown ANTHONY W THOMPSON business listings
DANA POINT, CA 92629 County Leave a message for ANTHONY W THOMPSON
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ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
4 TROVITA Map It Recorded: 04/15/2001 ANTHONY W THOMPSON business listings
IRVINE, CA 92620 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
2319 PAMELA LN Map It Recorded: 03/01/2006 ANTHONY W THOMPSON business listings
MODESTO, CA 95350 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
1005 CENTER AVE Map It Recorded: 08/25/2003 ANTHONY W THOMPSON business listings
ONTARIO, CA 91764 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON Born 1947 More Information on ANTHONY W THOMPSON
3311 MANDEVILLE PL Map It Recorded: 10/05/2004 ANTHONY W THOMPSON business listings
ORANGE, CA 92867 County **(714) 282-0410** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
(530) 226-5329 Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
2113 WESTERN OAK DR Map It Recorded: 03/12/2002 ANTHONY W THOMPSON business listings
REDDING, CA 96002 County Leave a message for ANTHONY W THOMPSON

www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
4327 LYNBROOK LOOP Map It Recorded: 10/05/2004 ANTHONY W THOMPSON business listings
REDDING, CA 96003 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
6945 GRANADA DR Map It Recorded: 11/17/1999 ANTHONY W THOMPSON business listings
REDDING, CA 96002 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON **Born Sep 1955** More Information on ANTHONY W THOMPSON
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ANTHONY W THOMPSON **Born Sep 1975** More Information on ANTHONY W THOMPSON
1735 REED AVE Map It Recorded: 03/12/2002 ANTHONY W THOMPSON business listings
SAN DIEGO, CA 92109 County **(619) 272-5984** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON **Born 1947** More Information on ANTHONY W THOMPSON
801 PARK CENTER DR Map It Recorded: 03/12/2002 ANTHONY W THOMPSON business listings
SANTA ANA, CA 92705 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON **Born 1975** More Information on ANTHONY W THOMPSON
1000 ESCALON AVE Map It Recorded: 02/01/2006 ANTHONY W THOMPSON business listings
SUNNYVALE, CA 94085 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
1375 INNISBROOK CIR Map It Recorded: 12/01/2005 ANTHONY W THOMPSON business listings
UPLAND, CA 91784 County Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

ANTHONY W THOMPSON More Information on ANTHONY W THOMPSON
1375 INNISBROOK CIR Map It Recorded: 01/01/2005 ANTHONY W THOMPSON business listings
UPLAND, CA 91784 County **(909) 982-9142** Leave a message for ANTHONY W THOMPSON
www.ZabaSearch.com/Google - Background Check

Can't find ANTHONY W THOMPSON?
TRY THIS DATABASE
Background Check on ANTHONY W THOMPSON
www.PeopleLookUp.com 20 Year History

Search by Phone Number Search by Social Security Number **Complet**
Search Any Full Name: Anthony W Thompson

ZABASEARCH **being described as "Google o**
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT J – print-out of the search results returned from the FreeKnowX and ZabaSearch search engines for inventor Cummings.

KnowX

KnowX Standard | KnowX Professional | Superior | RapSheets

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Open an Account

STANDARD Login

USER NAME

PASSWORD

go

Forgot Login Info? click here

Related Searches

Find more info on Marquis Cummings by researching:

- Business Background Check
- Business Relationships
- Real Estate
- Reverse Address

Other Searches:

- Marriage Records
- Divorce Records
- Experian Reports
- Assets $
- Professional Licenses

Visit Partner Sites:

- Birth and Death Certificates

Order certified birth, death, marriage, divorce certificates

The Ultimate People Finder

Searching: Name: **Marquis Cummings** | City: **Encinitas** | State: **CA** | Zip: **92024**

0 Matches Found

Try Address Verification - Updated Nightly.

NEW SEARCH MODIFY SEARCH

Example Record

NI

Try Know
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locate hai
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determine
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more.

No matches were found.

Search Again for Free Using These Tips:

- Search for individuals in the U.S. only.
- Check spelling
- Avoid full middle names (middle initial may be listed)
- Search head-of-the-household name where possible
- If searching for a female, try a first initial and last name
- Avoid abbreviations (Mil will not expand to find Miller, Milken, Milton, etc.)
- If unsure of the exact city name, just enter the state
- Enter complete 5-digit zip code (partial number will not work)
- For more tips, go to our search tips

First Name: Marquis

Last Name: Cummings

City: Encinitas

State: California

Zip: 92024 Search

Company Info | Public Records Info | Privacy Statement | Privacy at ChoicePoint | Legal

Search by Phone Number Search by Social Security Number **Complete**

ZABASEARCH **Search Any Full Name:** Marquis Cummings
Advanced Search

Public Information **Results Summary:** 4 MARQUIS CUMMINGS Leave a message Check mess

MARQUIS CUMMINGS - 4 Listings
Leave a message for Marquis Cummings Check messages E-mail This Page ZabaAlert
Check messages for: Cummings - Marquis - Marquis Cummings Check YouTube

MARQUIS CUMMINGS More Information on MARQUIS CUMMINGS
6490 RAINBOW HEIGHTS RD Map It Recorded: 04/15/2001 MARQUIS CUMMINGS business listings
FALLBROOK, CA 92028 County Leave a message for MARQUIS CUMMINGS
www.ZabaSearch.com/Google - Background Check

MARQUIS L CUMMINGS More Information on MARQUIS L CUMMINGS
42751 STATE HWY 74 Map It Recorded: 02/26/2003 MARQUIS L CUMMINGS business listings
HEMET, CA 92544 County Leave a message for MARQUIS L CUMMINGS
www.ZabaSearch.com/Google - Background Check

MARQUIS L CUMMINGS **Born Jun 1938** More Information on MARQUIS L CUMMINGS
220 MEMPHIS AVE Map It Recorded: 11/17/1999 MARQUIS L CUMMINGS business listings
HUNTINGTON BEACH, CA 92648 County Leave a message for MARQUIS L CUMMINGS
www.ZabaSearch.com/Google - Background Check

MARQUIS L CUMMINGS **Born Jun 1938** More Information on MARQUIS L CUMMINGS
509 7TH ST Map It Recorded: 05/21/2003 MARQUIS L CUMMINGS business listings
HUNTINGTON BEACH, CA 92648 County Leave a message for MARQUIS L CUMMINGS
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Search by Phone Number Search by Social Security Number **Complete Backgro**
Search Any Full Name: Marquis Cummings All Sta
Advanced Search

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT K – print-out of the search results returned from the FreeKnowX and ZabaSearch search engines for inventor Edwards.

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Open an Account

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USER NAME

PASSWORD

go

Forgot Login Info? click here

411 Directory

New Internet 411 Directory - phone listings updated nightly.

Searching: First Name: James
Edwards | Address: 8723 Hesby Cou
Diego | State: CA

0 Matches Found

For more matches, search our Real Estate listings!

NEW SEARCH MODIFY SEARCH

E

No matches were found.
Please see the search tips, or modify your search.

Please check the coverage area for source and effective date information.

Related Searches

Find more info on James Edwards by researching:

- Business Background Check
- Business Relationships
- Real Estate
- Reverse Address

Other Searches:

- Marriage Records
- Divorce Records
- Experian Reports
- Assets $
- Professional Licenses

Company Info | Public Records Info | Privacy Statement | Privacy at ChoicePoint | Legal

Search by Phone Number Search by Social Security Number **Complete**

ZABASEARCH **Search Any Full Name:** James P. Edwards

Search Advanced Search

Public Information **Results Summary:** 14 JAMES P EDWARDS Leave a message Check mess

JAMES P. EDWARDS - Background Check, 20 Year History Premium Listing
www.Intelius.com Comprehensive Report. Criminal Records. Latest Contact Information.

Find JAMES P. EDWARDS Premium Listing
www.Intelius.com Get Current Phone and Address

JAMES P EDWARDS - 14 Listings
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Check messages for: Edwards - James - James P. Edwards Check YouTube

More Information on JAMES P EDWARDS

www.ZabaSearch.com/Google -

JAMES P EDWARDS **Born Mar 1961** More Information on JAMES P EDWARDS
2265 WOODHOLLOW LN Map It Recorded: Unknown JAMES P EDWARDS business listings
CHINO HILLS, CA 91709 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born 1961** More Information on JAMES P EDWARDS
150 SAVONA WALK Map It Recorded: Unknown JAMES P EDWARDS business listings
LONG BEACH, CA 90803 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS More Information on JAMES P EDWARDS
24350 SWEETSHADE LN Map It Recorded: 03/12/2002 JAMES P EDWARDS business listings
NEWHALL, CA 91321 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS More Information on JAMES P EDWARDS
8715 A ST Map It Recorded: Unknown JAMES P EDWARDS business listings
OAKLAND, CA 94621 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born Jun 1937** More Information on JAMES P EDWARDS
16753 POWER LINE RD Map It Recorded: 07/22/2003 JAMES P EDWARDS business listings
REDDING, CA 96001 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born Jun 1937** More Information on JAMES P EDWARDS
16753 POWER LINE RD Map It Recorded: Unknown JAMES P EDWARDS business listings
REDDING, CA 96001 County **(530) 243-7133** Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born May 1966** More Information on JAMES P EDWARDS
19523 LORNE ST Map It Recorded: 01/25/2002 JAMES P EDWARDS business listings
RESEDA, CA 91335 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born 1960** More Information on JAMES P EDWARDS

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1621 MARSHFIELD CT Map It Recorded: Unknown JAMES P EDWARDS business listings
SALINAS, CA 93906 County Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born 1964** More Information on JAMES P EDWARDS
8723 HESBY CT Map It Recorded: Unknown JAMES P EDWARDS business listings
SAN DIEGO, CA 92129 County **(858) 538-9045** Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born Sep 1960** More Information on JAMES P EDWARDS
8723 HESBY CT Map It Recorded: 06/23/2004 JAMES P EDWARDS business listings
SAN DIEGO, CA 92129 County **(858) 538-9045** Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born Sep 1960** More Information on JAMES P EDWARDS
8723 HESBY CT Map It Recorded: 03/10/2004 JAMES P EDWARDS business listings
SAN DIEGO, CA 92129 County **(858) 538-9045** Leave a message for JAMES P EDWARDS
www.ZabaSearch.com/Google - Background Check

JAMES P EDWARDS **Born 1947** More Information on JAMES P EDWARDS
4760 EMIL RD Map It Recorded: 07/30/2003 JAMES P EDWARDS business listings
SHINGLE SPRINGS, CA 95682 County **(530) 676-2214** Leave a message for JAMES P EDWARDS

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JAMES P EDWARDS More Information on JAMES P EDWARDS
30732 VIA NORTE Map It Recorded: Unknown JAMES P EDWARDS business listings
TEMECULA, CA 92591 County Leave a message for JAMES P EDWARDS
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Search by Phone Number Search by Social Security Number **Complete Backgro**
Search Any Full Name: James P. Edwards All Sta
Advanced Search

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Lin Zhi *et al.*	Art Unit	:	1623
Serial No.	:	10/080,503	Examiner	:	Lawrence E. Crane, Ph.D.
Conf. No.	:	8671	Customer No.:		20985
Filed	:	February 22, 2002			
Title	:	**TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**			

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 1 – a copy of the substitute DECLARATION.

DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled

TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

( ) is attached hereto.
(X) was filed by an authorized person on my behalf on February 22, 2002 as Application Serial No. 10/080,503
(X) was amended on January 31, 2005, November 3, 2005, May 19, 2006, and by Examiner's amendment of July 11, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

Number	Country	Day/Month/Year Filed	Priority Claimed (Yes or No)
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
60/271,115	February 23, 2001

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
N/A		

PCT Application No.	Filing Date	Status
N/A		

We hereby declare that all statements made therein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Full name of joint inventor: Robert I. Higuchi

Inventor's signature: ______________________

Date: ______________________

Residence: 434 Marview Drive
San Diego, CA 92075

Citizenship: U.S.A

Full name of joint inventor: Lin Zhi

Inventor's signature: ______________________

Date: ______________________

Residence: 3988 Via Cangrejo
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: ______________________

Date: ______________________

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ______________________

Date: ______________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ______________________

Date: ______________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ______________________

Date: ______________________

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Jyun-Hung Chen

Inventor's signature: ______________________

Date: ______________________

Residence: 7614 Palmilla Drive, #58
San Diego, CA 92122

Citizenship: Taiwan

Full name of joint inventor: Marquis L. Cummings

Inventor's signature: ______________________

Date: ______________________

Residence: 917 Bracero Road
Encinitas, CA 92024

Citizenship: U.S.A.

Full name of joint inventor: James P. Edwards

Inventor's signature: ______________________

Date: ______________________

Residence: 8723 Hesby Court
San Diego, CA 92129

Citizenship: U.S.A.

Full name of joint inventor: Mark E. Adams

Inventor's signature: ______________________

Date: ______________________

Residence: 12638 Carmel Country Road, #130
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor:	Charlotte L.F. Deckhut
Inventor's signature:	______________________________
Date:	______________________________
Residence:	3105 Kalmia Street San Diego, CA 92104
Citizenship:	U.S.A.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 2 – copies of the letter, original specification, amendments made during prosecution and the substitute DECLARATION sent to inventor Caferro.

FISH & RICHARDSON P.C.

12390 El Camino Real
San Diego, California
92130

Telephone
858 678-5070

Facsimile
202 626-7796

Web Site
www.fr.com

Stephanie Seidman
(858) 678-4777

Email
seidman@fr.com

October 30, 2006

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Thomas R. Caferro
101 Thorton Green Pl.
Holly Springs, NC 27540

Re: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Applicant:	**Lin Zhi *et al.***
Application No.:	**10/080,503**
Filing Date:	**February 22, 2002**
Country:	**United States**
Your Ref.:	**016-0082.A.US**
Our Ref.:	**18202-018001/1082**

Dear Mr. Caferro:

Enclosed is a Declaration for Patent Application for your execution. The above-captioned patent application was prepared and filed with the U.S. Patent and Trademark Office on February 22, 2002. This patent application has been deemed allowable. The Examiner has required a replacement Declaration because the hand-annotated address changes made by one of the inventors was not initialed on the originally submitted Declaration.

We also have enclosed a copy of the application as filed with the U.S. Patent and Trademark Office for your review. Also enclosed are copies of the Amendments that have been filed during prosecution of this patent application. Please review the application and the amendments.

After reviewing the application and the amendments, please sign and date the enclosed Declaration for Patent Application and return the executed document to our office as soon as possible. For your convenience we have enclosed a stamped, self-addressed envelope for use in returning the executed document to us.

In the event that the enclosed Declaration for Patent Application is incorrect in anyway, please mark through the error(s), type or print the correction(s) above it, and then ***initial*** **and** ***date*** in the margin beside the correction(s).

We would appreciate the prompt execution and return of the enclosed Declaration for Patent Application. If you have any questions, please do not hesitate to contact our office.

Sincerely,

Stephanie Seidman

SLS/tes
Enclosures
1067870?.doc

DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled

TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

( ) is attached hereto.
(X) was filed by an authorized person on my behalf on February 22, 2002 as Application Serial No. 10/080,503
(X) was amended on January 31, 2005, November 3, 2005, May 19, 2006, and by Examiner's amendment of July 11, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

Number	Country	Day/Month/Year Filed	Priority Claimed (Yes or No)
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
60/271,115	February 23, 2001

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
N/A		

PCT Application No.	Filing Date	Status
N/A		

We hereby declare that all statements made therein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Full name of joint inventor: Robert I. Higuchi

Inventor's signature: ______________________

Date: ______________________

Residence: 434 Marview Drive
San Diego, CA 92075

Citizenship: U.S.A

Full name of joint inventor: Lin Zhi

Inventor's signature: ______________________

Date: ______________________

Residence: 3988 Via Cangrejo
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: ________________

Date: ________________

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ________________

Date: ________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ________________

Date: ________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ________________

Date: ________________

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Jyun-Hung Chen

Inventor's signature: ______________________________

Date: ______________________________

Residence: 7614 Palmilla Drive, #58
San Diego, CA 92122

Citizenship: Taiwan

Full name of joint inventor: Marquis L. Cummings

Inventor's signature: ______________________________

Date: ______________________________

Residence: 917 Bracero Road
Encinitas, CA 92024

Citizenship: U.S.A.

Full name of joint inventor: James P. Edwards

Inventor's signature: ______________________________

Date: ______________________________

Residence: 8723 Hesby Court
San Diego, CA 92129

Citizenship: U.S.A.

Full name of joint inventor: Mark E. Adams

Inventor's signature: ______________________________

Date: ______________________________

Residence: 12638 Carmel Country Road, #130
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Charlotte L.F. Deckhut

Inventor's signature: ______________________________

Date: ______________________________

Residence: 3105 Kalmia Street
San Diego, CA 92104

Citizenship: U.S.A.

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Restricted Delivery Fee (Endorsement Required)	
Total Postage & Fees	$

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USPS
OCT 30 2006

7005 1820 0006 3811 8617

Sent To Thomas R. Caferro
Street, Apt. No.; or PO Box No. 101 Thorton Greens Pl.
City, State, ZIP+4 Holly Springs, NC 27540

PS Form 3800, June 2002 See Reverse for Instructions

TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Related Application

The present application claims the benefit of priority to U.S. Provisional Application No. 60/271,115, filed on February 23, 2001 which is incorporated by reference in its entirety.

Field of the Invention

This invention relates to non-steroidal compounds that are modulators (*i.e.* agonists and antagonists) of androgen receptors and to methods for making and using such compounds.

Background of the Invention

Intracellular receptors (IRs) form a class of structurally-related genetic regulators scientists have named "ligand dependent transcription factors." R.M. Evans, *Science*, 240:889 (1988). Steroid receptors are a recognized subset of the IRs, including the progesterone receptor (PR) androgen receptor (AR), estrogen receptor (ER), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Regulation of a gene by such factors requires both the IR itself and a corresponding ligand, which has the ability to selectively bind to the IR in a way that affects gene transcription.

A compound that binds an IR and mimics the effect of the native ligand is referred to as an "agonist", while a compound that inhibits the effect of the native ligand is called an "antagonist." The term "modulators" refers to compounds that are agonists, partial agonists or antagonists.

The effectiveness of known modulators of steroid receptors is often tempered by their undesired side-effect profile, particularly during long-term administration. For example, the effectiveness of progesterone and estrogen agonists, such as norgestrel and diethylstilbesterol, respectively, as female birth control agents must be weighed against the increased risk of breast cancer and heart disease to women taking such agents. Similarly, the progesterone

antagonist, mifepristone (RU486), if administered for chronic indications, such as uterine fibroids, endometriosis and certain hormone-dependent cancers, could lead to homeostatic imbalances in a patient due to its inherent cross-reactivity as a GR antagonist. Accordingly, identification of compounds that have good specificity for one or more steroid receptors, but have reduced or no cross-reactivity for other steroid or intracellular receptors, would be of significant value in the treatment of male and female hormone responsive diseases.

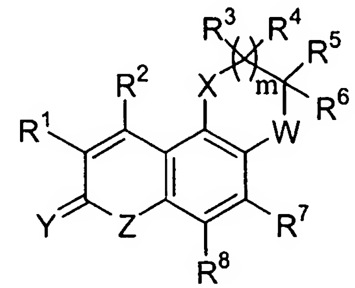
A group of quinolinone and coumarin analogs having a fused ring system of the aryl, piperidine, pyrrolidine, or indoline series have been described as androgen modulators. See U. S. Patent No. 5,696,130; Int. Patent Appl. WO 97/49709; L.G. Hamann, *et al. J. Med. Chem.*, 41:623-639 (1998); J. P. Edwards, *et al.*, *Bioorg. Med. Chem. Lett.*, 8:745-750 (1998); J. P. Edwards, *et al.*, *Bioorg. Med. Chem. Lett.*, 9:1003-1008 (1999), R. I. Higuchi, *et al.*, *Bioorg. Med. Chem. Lett.*, 9:1335-1340 (1999).

The entire disclosures of the publications and references referred to above and hereafter in this specification are incorporated herein by reference and are not admitted to be prior art.

Summary of the Invention

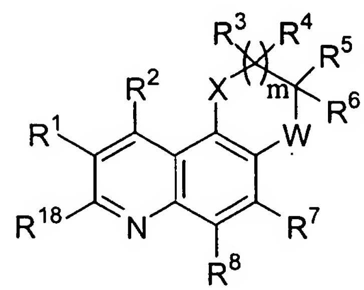
The present invention is directed to androgen receptor modulator compounds. This invention is also directed to pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating processes mediated by steroid receptors. More particularly, the invention relates to non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and antagonists for androgen receptors (AR). Also provided are methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis.

Compounds of the present invention are represented by those having the formula:



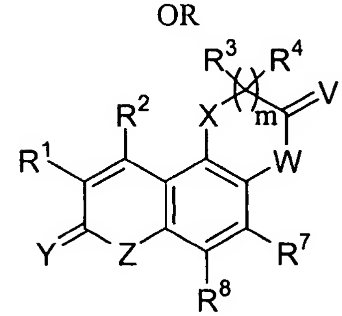
(I)

OR



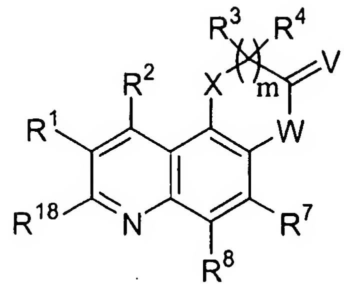
(II)

OR



(III)

OR



(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^9 is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{10} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$, wherein the

alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{11} and R^{12} each independently is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{13} is selected from the group of $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

R^{16} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{17} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{16}R^{17}$, SOR^{17} and SO_2R^{17}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{19} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, N{R^{11}}, N{C(Y)R^{11}}, N{SO_2R^{12}} and N{S(O)R^{12}}; and

Y is selected from the group of O, S, N{R^{19}} and N{OR^{19}};

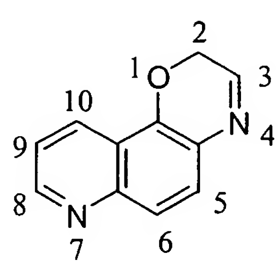
and pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

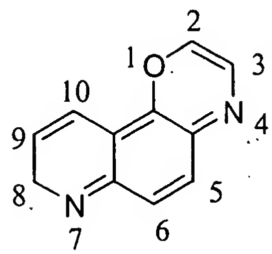
In accordance with the present invention, we have developed novel compounds, compositions and methods of preparing non-steroidal compounds that are AR modulators. Specifically, we have developed agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and antagonists for androgen receptors and methods of preparing these compounds and compositions. Compounds of the present invention may be high affinity, high specificity agonists, partial agonists, or antagonists for androgen receptors.

In accordance with the present invention and as used herein, the following structure definitions are provided for nomenclature purposes. Furthermore, in an effort to maintain consistency in the naming of compounds of similar structure but differing substituents, the compounds described herein are named according to the following general guidelines. The numbering system for the location of substituents on such compounds is also provided.

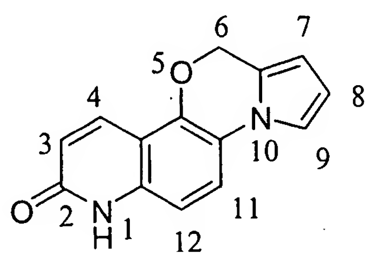
A **2*H*-[1,4]oxazino[2,3-*f*]quinoline** is represented by the following structure:



An **8*H*-[1,4]oxazino[2,3-*f*]quinoline** is represented by the following structure:



A **1H, 6H-pyrrolo[1',2':4,5][1,4]oxazino[2,3-f]quinolin-2-one** is represented by the following structure:



In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to

about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl and the like.

The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon tyriple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

The term "heteroalkyl" refers to alkyl groups, as described above, in which one or more skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof. The term heteroalkyl also includes alkyl groups in which one 1 to about 6 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof, as well as those in which 1 to 4 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof and those in which 1 to 2 skeletal atoms are oxygen, nitrogen, sulfur or combinations thereof.

The term "alkoxy," alone or in combination, refers to an alkyl ether radical wherein the term alkyl is defined as above. Examples of alkoxy radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

The term "aryloxy," alone or in combination, refers to an aryl ether radical wherein the term aryl is defined as below. Examples of aryloxy radicals include phenoxy, benzyloxy and the like.

The term "alkylthio," alone or in combination, refers to an alkyl thio radical wherein the term alkyl is defined as above.

The term "arylthio," alone or in combination, refers to an aryl thio radical wherein the term aryl is defined as below.

The term "oxo" refers to =O.

The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from six to about twenty carbon atoms. The term

aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

The term "heteroaryl" refers to optionally substituted aromatic ring systems containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidoyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

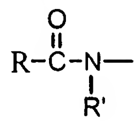
The term "heteroarylalkyl" refers to a C_1-C_4 alkyl group containing a heteroaryl group, each of which may be optionally substituted.

The term "heteroarylthio" refers to the group -S-heteroaryl.

The term "acyloxy" refers to the ester group –OC(O)-R, where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, or arylalkyl, wherein the alkyl, alkenyl, alkynyl and arylalkyl groups may be optionally substituted.

The term "carboxy esters" refers to –C(O)OR where R is alkyl, aryl or arylalkyl, wherein the alkyl, aryl and arylalkyl groups may be optionally substituted.

The term “carboxamido” refers to



where R and R' each independently is selected from the group of hydrogen, alkyl, aryl and arylalkyl, wherein the alkyl, aryl and arylalkyl groups may be optionally substituted.

The term “cycloalkyl”, alone or in combination, refers to a monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has from 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term “arylalkyl,” alone or in combination, refers to an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The terms haloalkyl, haloalkenyl, haloalkynyl and haloalkoxy include alkyl, alkenyl, alkynyl and alkoxy structures, as described above, that are substituted with one or more fluorines, chlorines, bromines or iodines, or with combinations thereof.

The terms cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl include optionally substituted cycloalkyl, aryl, arylalkyl, heteroaryl, alkyl, alkynyl, alkenyl, haloalkyl and heteroalkyl groups.

The term “carbocycle” includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which all of the skeletal atoms are carbon.

The term “heterocycle” includes optionally substituted, saturated or unsaturated, three- to eight-membered cyclic structures in which one or more skeletal atoms is oxygen, nitrogen, sulfur, or combinations thereof.

The term “acyl” includes alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl substituents attached to a compound *via* a carbonyl functionality (*e.g.*, -CO-alkyl, -CO-aryl, -CO-arylalkyl or -CO-heteroarylalkyl, *etc.*).

“Optionally substituted” groups may be substituted or unsubstituted. The substituents of an “optionally substituted” group may include, without limitation, one or more substituents

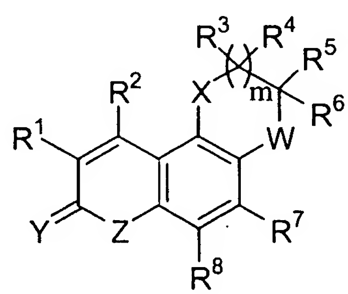
independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

The term "halogen" includes F, Cl, Br and I.

The term "mediate" means affect or influence. Thus, for example, conditions mediated by an androgen receptor are those in which an androgen receptor plays a role. Androgen receptors are known to play a role in conditions including, for example, acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, and hormone-dependent cancers.

The term "selective" refers to compounds that display reactivity towards a particular receptor (e.g., an androgen receptor) without displaying cross-reactivity towards another receptor (e.g., glucocorticoid receptor). Thus, for example, selective compounds of the present invention may display reactivity towards androgen receptors without displaying cross-reactivity towards glucocorticoid receptors.

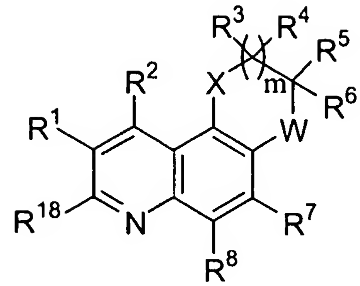
Compounds of the present invention are represented by those having the formula:



(I)

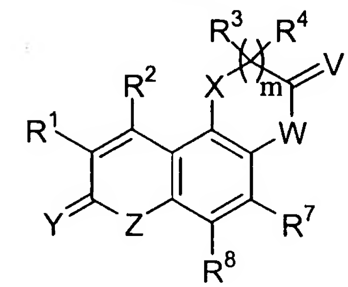
SDILIB1\RP02\428426.01

OR



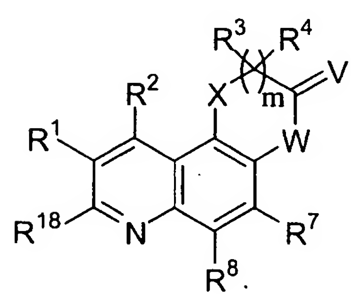
(II)

OR



(III)

OR



(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^9 is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{10} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{11} and R^{12} each independently is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{13} is selected from the group of $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

In another aspect, the present invention provides a method of modulating processes mediated by ARs by administering to a patient an effective amount of a compound of formula I through IV shown above, wherein R^1 through R^{13}, R^{16} through R^{19}, m, n, V, W, X, Y, and Z are as described above. In one aspect, the modulation is activation, while in another aspect, the modulation is inhibition. In each case, the method involves administering to a patient a pharmaceutically effective amount of a compound of formula I through IV shown above, wherein R^1 through R^{13}, R^{16} through R^{19}, m, n, V, W, X, Y, and Z are as described above.

With regard to the foregoing variables, the inventors contemplate any combination of the Markush groups as set forth above and as described in the following table.

Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^1	hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl may be optionally substituted.	hydrogen, F and optionally substituted $C_1 - C_4$ alkyl.	hydrogen and optionally substituted $C_1 - C_4$ alkyl
R^2	hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ hetero-alkyl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, hetero-alkyl, alkynyl and alkenyl groups may be optionally substituted	hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.	hydrogen, $C_1 - C_2$ alkyl, $C_1 - C_2$ haloalkyl and $C_1 - C_2$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.	CF_3

R^{16} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{17} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{16}R^{17}$, SOR^{17} and SO_2R^{17}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{19} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is selected from the group of O, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$;

and pharmaceutically acceptable salts thereof.

In one aspect, the present the invention provides compounds represented by formula I through IV. In another aspect, the present invention provides a pharmaceutical composition comprising an effective amount of an AR modulating compound of formula I through IV shown above, wherein R^1 through R^{13}, R^{16} through R^{19}, m, n, V, W, X, Y, and Z are as described above.

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^3	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$	hydrogen
	R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring	R^3 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic ring		
R^4	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_2$ alkyl	hydrogen and methyl	hydrogen

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^5	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl, $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein said alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and CF_3
R^6	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, $C_2 - C_4$ alkynyl and $C_2 - C_4$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, alkynyl and alkenyl groups may be optionally substituted	hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_4$ alkyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
	R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring	aryl, arylalkyl and heteroaryl, wherein the aryl, arylalkyl and heteroaryl groups may be optionally substituted	R^3 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic ring	
	R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring		R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring	R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring
R^7	hydrogen, F, Cl, Br, I, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted	hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_2$ alkyl	hydrogen and methyl
	OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$			

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^8	hydrogen, F, Cl, Br, I, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted	hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_2$ alkyl	hydrogen and methyl
	OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$			
R^9	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_4$ alkyl	hydrogen and methyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{10}	hydrogen, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12}, $S(O)R^{12}$, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$ and CO_2R^{12}	hydrogen and methyl
R^{11}	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and methyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{12}	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl, and heteroalkyl groups may be optionally substituted	hydrogen and methyl

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{13}	CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkenyl, $C_2 - C_6$ alkynyl, $C_3 - C_6$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted	CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, $C_2 - C_4$ alkenyl and aryl wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and aryl groups may be optionally substituted	$C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropyl-methyl and allyl
	R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring	R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring	R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring	R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{16}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted C_1-C_4 alkyl	hydrogen and methyl
R^{17}	hydrogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl and C_1-C_6 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted C_1-C_4 alkyl	hydrogen and methyl
R^{18}	hydrogen, F, Cl, CN, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, SOR^{17} and SO_2R^{17}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen, F, Cl, OR^{16}, SR^{16} and $NR^{16}R^{17}$	H, F, Cl and OR^{16}

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R^{19}	hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkenyl and $C_2 - C_6$ alkynyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and alkynyl groups may be optionally substituted	hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted	hydrogen and optionally substituted $C_1 - C_4$ alkyl	hydrogen and methyl
m	0 and 1	1	0	
V	S	O		
W	NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$	NH and $N\{R^{13}\}$		
X	O, S, NH and $N\{R^{11}\}$	O and S	O	S
Y	O and S	O	S	
Z	NH, $N\{R^{11}\}$ and O	NH and $N\{R^{11}\}$		

The compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, but are not limited to, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, tris(hydroxymethyl)aminomethane and the like and suitable combinations of

any two or more thereof. Additional pharmaceutically acceptable salts are known to those skilled in the art.

AR agonist, partial agonist and antagonist compounds (including compounds with tissue-selective AR modulator activity) of the present invention may be useful in the treatment of process(es) mediated by androgen receptor(s), including acne (antagonist), male-pattern baldness (antagonist), male hormone replacement therapy (agonist), sexual dysfunction (agonist), wasting diseases (agonist), hirsutism (antagonist), stimulation of hematopoiesis (agonist), hypogonadism (agonist), prostatic hyperplasia (antagonist), osteoporosis (agonist), male contraception (agonist), impotence (agonist), cancer cachexia (agonist), various hormone-dependent cancers (*e.g.*, prostate cancer (antagonist), breast cancer and the like), process(es) requiring anabolic agents (agonist) and the like. It is understood by those of skill in the art that a partial agonist may be used where agonist activity is desired, or where antagonist activity is desired, depending upon the AR modulator profile of the particular partial agonist.

It is understood by those skilled in the art that while the compounds of the present invention will typically be employed as selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is desirable. For example, use of a PR agonist (*i.e.*, progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare-ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare-ups that occur.

Furthermore, it is understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation,

chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

Representative AR modulator compounds (i.e., agonists and antagonists) according to the present invention include: (3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **101**); (3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **102**); (3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **103**); (3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **104**); (3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **105**); (3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **106**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **107**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **108**); (3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **109**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **110**); (3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **111**); (3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **112**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **113**); (3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **114**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **115**); (3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **116**); (3*R/S*)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **117**); (3*R/S*)-

4-Ethyl-2,3,4,7-tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **118**); (3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **119**); (3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **120**); (3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **121**); (3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **122**); (3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **123**); (3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **124**); (3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **125**); (3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **126**); (3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **127**); (3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **128**); (3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **129**); (3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **130**); 2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **131**); 2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **132**); (7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **133**); (7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **134**); (7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **135**); (±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-

f]quinolin-8-one (Compound **136**); (7*R*)-6,6a,7,8,9,10-Hexahydro-4-(trifluoromethyl)-1*H*-pyrrolo[1',2':4,5][1,4]oxazino[2,3-*f*]quinolin-2-one (Compound **137**); 2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **138**); (3*R*)-8-Chloro-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Compound **139**); (3*R*) -3-Ethyl-3,4-dihydro-8-isopropoxy-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Compound **140**); (±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **141**); (–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **142**); (+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **143**).

Within such group, representative compounds include: 3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **104**); (3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **110**); (3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **111**); (3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **112**); (3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **123**); (3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **124**); (3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **125**); (7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **134**); (7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **133**); (±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-

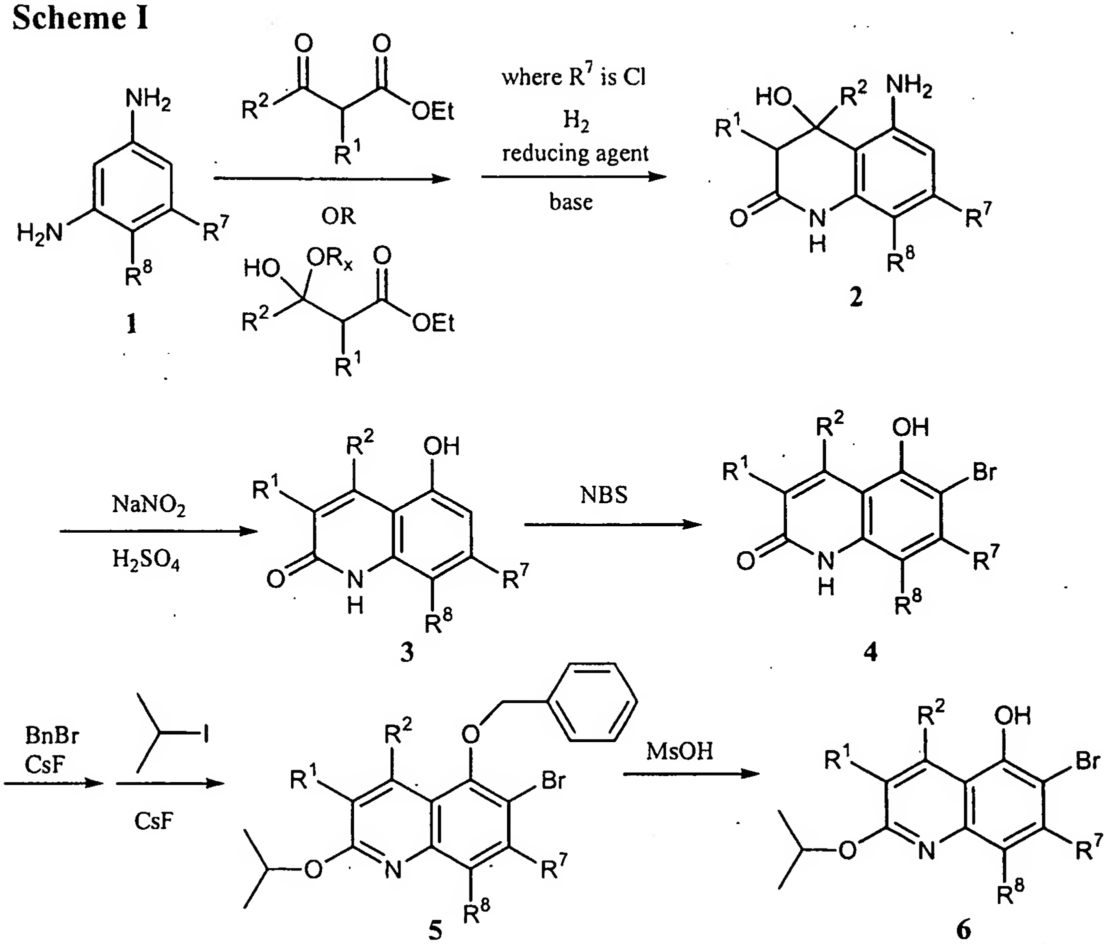
[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **136**); (±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **141**); (–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **142**); (+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **143**); (±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **144**); (±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **145**); (±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **146**); (±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **147**); (-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **148**); (+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **149**); (±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **150**); (3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **151**); (3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **152**); (±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **153**); (3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **154**); (3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **155**).

Compounds of the present invention, comprising classes of heterocyclic nitrogen compounds and their derivatives, can be obtained by routine chemical synthesis, *e.g.*, by

modification of the heterocyclic nitrogen compounds disclosed or by a total synthesis approach.

The sequences of steps for several general schemes to synthesize the compounds of the present invention are shown below. In each of the schemes the R groups (*e.g.*, R^1, R^2, etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulas I through IV also comprise potential substituents for the analogous positions on the structures within the schemes.

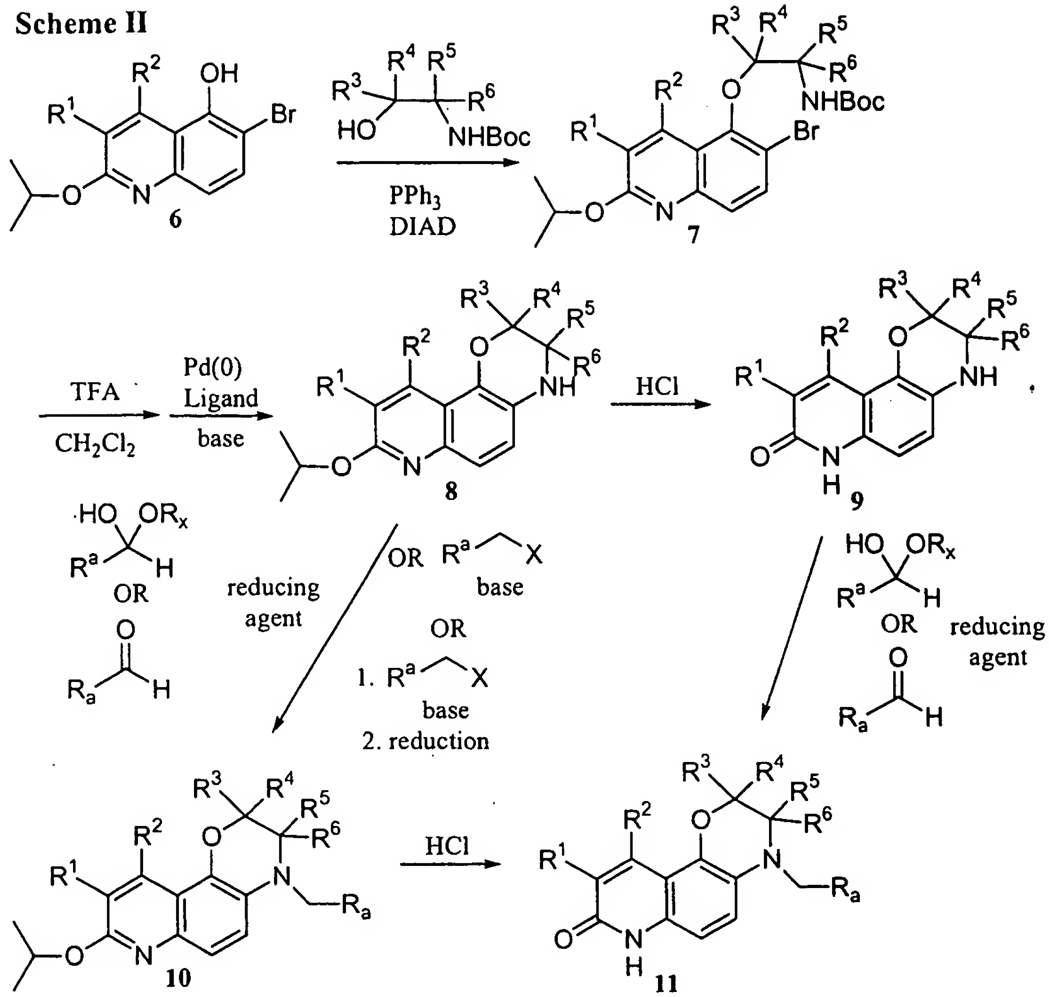
Scheme I



A synthesis of an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one compound (*e.g.*, structures **9** and **11**), is depicted in **Schemes I** and **II**. The process of **Scheme I** begins with the Knorr cyclization of a phenylenediamine derivative, for example, 5-chloro-1,3-phenylenediamine (structure **1**), with a β-ketoester, or its corresponding hydrate or hemiacetal, for example ethyl 4,4,4-trifluoroacetoacetate, to afford the corresponding (1*H*)-quinolin-2-one. See G, Jones, *Comprehensive Heterocyclic Chemistry,* Katritzky, A. R.; Rees, C. W., eds. Pergamon, New York, 1984. Vol. 2, chap. 2.08, pp 421-426, the disclosure of which is herein incorporated by reference. Reduction of the halide group could be achieved by chemical reduction, with, for example, a metal catalyst, for example, 10% Pd-C, in a hydrogen atmosphere, to afford a compound of structure **2**. Conversion of the aniline to a phenol could be effected by treatment of structure **2** with a diazotizing agent, for example, sodium nitrite in sulfuric acid, to afford a compound of structure **3**. Bromination of the phenol with a brominating reagent, for example, *N*-bromosuccinimide, in the presence of a base, for example, diisopropylamine, affords a compound of structure **4**. See S. Fujisaki, *et. al., Bull. Chem. Soc. Jpn.* **1993**, *66*, 1576-1579, the disclosure of which is herein incorporated by reference.

Selective protection of the phenolic oxygen could be achieved by treatment of structure **4** with an alkyl halide, for example, benzyl bromide, in the presence of a base, for example, cesium fluoride, to afford the corresponding ether. Protection of the pyridone ring, with, for example isopropyl iodide, mediated by a base, for example, cesium fluoride, affords the corresponding imino ether (structure **5**). Selective hydrolysis of the phenolic ether could be accomplished by acidic hydrolysis, with, for example, a 1:1 mixture of methanesulfonic acid and acetic acid, to afford a phenol of structure **6**.

Scheme II

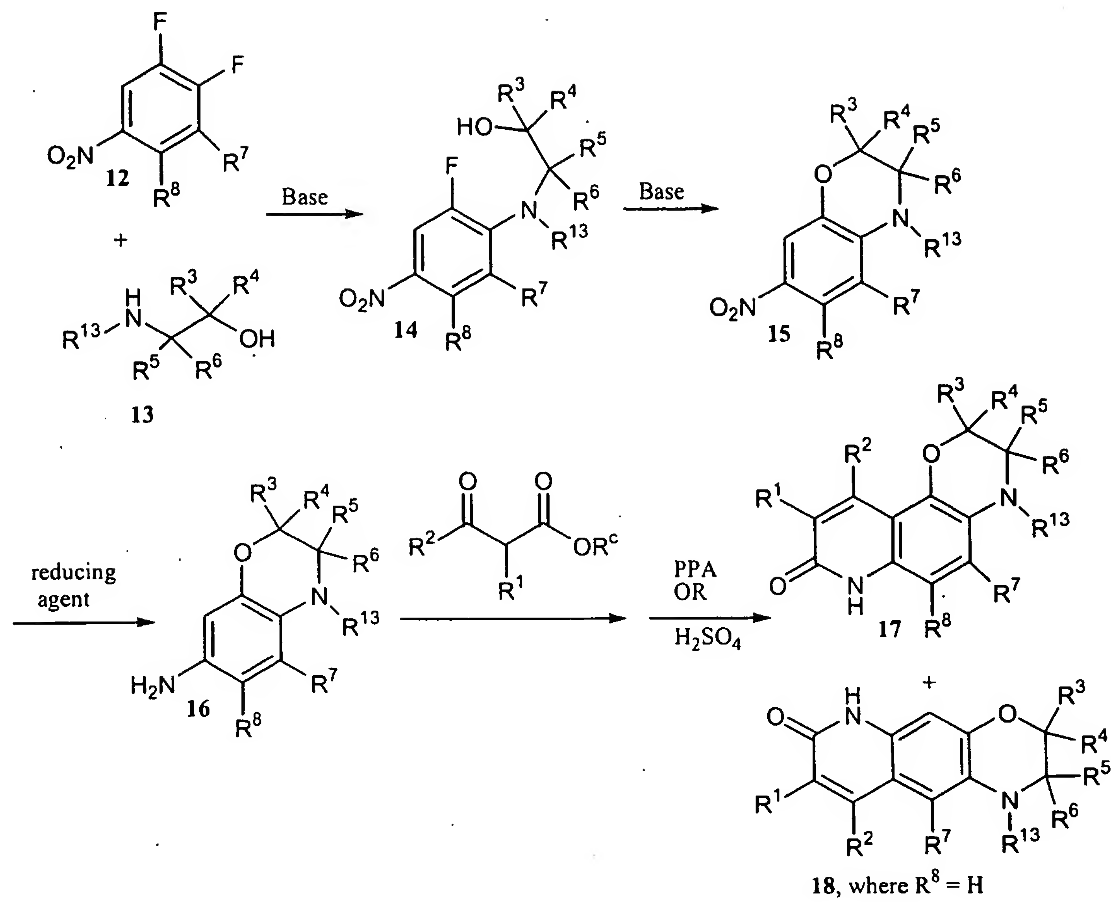


The following transformations are illustrated in **Scheme II**. Alkylation of the phenolic oxygen was accomplished by treatment of the phenol with a protected amino alcohol, for example, (*R*)-*N*-*t*-boc-alinol, under Mitsunobu conditions, for example, triphenylphosphine and diisopropyl azodicarboxylate, in the presence of a base, for example, *N*-methylmorpholine, to afford the corresponding Mitsunobu product. Removal of the *t*-butoxycarbonyl protecting group can be accomplished by acidic hydrolysis, with, for example, trifluoroacetic acid, to afford a compound of structure **7** (**Scheme II**). Closure of the amine to the aromatic halide can be achieved by treatment of compound with a transition

metal, for example $Pd_2(dba)_3$ in the presence of a ligand, for example, BINAP, and a base, for example, sodium *t*-butoxide, to afford a compound of structure **8**. See S. Wagaw, *et. al., J. Am. Chem. Soc.* **1997**, *119*, 8451-8458, the disclosure of which is herein incorporated by reference. Treatment of a compound of structure **8** with an acid, for example hydrochloric acid in acetic acid, at elevated temperatures, affords an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one of structure **9**. Alternatively, treatment of a compound of structure **8** with an aldehyde or its corresponding hydrate or hemiacetal, for example, trifluoroacetaldehyde hemiacetal, in the presence of a reducing agent, for example, sodium cyanoborohydride, in a carboxylic acid, for example, trifluoroacetic acid, affords a compound of structure **10**. Alternatively, alkylation could be achieve by alkylation of structure **8** with an alkyl halide, for example, allyl bromide, mediated by a base, for example potassium carbonate, to afford a compound of structure **10**. Treatment of a compound of structure **10** with an acid, for example hydrochloric acid in acetic acid, affords an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one, a compound of structure **11**. Alternatively, treatment of a compound of structure **9** with an aldehyde or its corresponding hydrate or hemiacetal, for example, cyclopropylmethylcarboxaldehyde, in the presence of a reducing agent, for example, sodium cyanoborohydride, in a carboxylic acid, for example, acetic acid, affords a compound of structure **11**.

An enantiomer of structures **9** or **11**, or a racemic mixture may be obtained by the synthetic route as described in **Scheme II**, by starting with the enantiomer of the *β*-aminoalcohol as shown (*e.g.*, an (*S*)-*β*-amino alcohol), or a racemic mixture of the *β*-aminoalcohol shown (*e.g.*, a ($\pm$)-*β*-amino alcohol. Accordingly, an (*S*)-*β*-amino alcohol, employed in **Scheme II,** produces an (*S*)-quinolinone; an (*R*)-*β*-amino alcohol, employed in **Scheme II**, produces an (*R*)-quinolinone; and a racemic mixture of the *β*-amino alcohol, employed in **Scheme II**, produces a racemic mixture of the corresponding quinolinone. A racemic mixture of quinolinones could be separated into its corresponding enantiomers by separation on chiral HPLC with, for example, a chirapak AS column eluted with hexanes:ethanol.

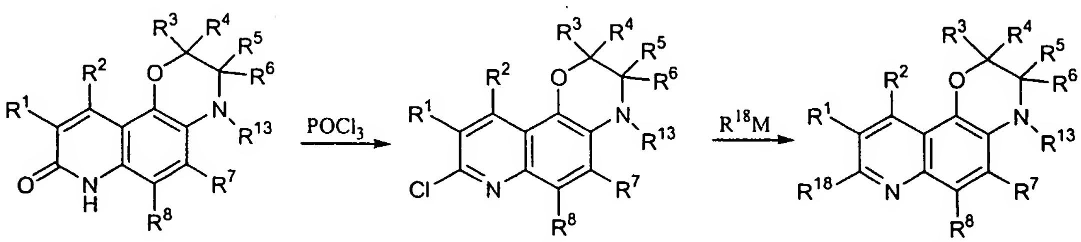
Scheme III



The asymmetric synthesis in **Scheme III** begins with the chemo- and regioselective *N*-alkylation of a β-aminoalcohol, either as a single enantiomer (*R* or *S*) or its racemate, for example, *(R)*-prolinol, onto a 3,4-dihalonitrobenzene, for example, 3,4-difluoronitrobenzene, mediated by a base, for example, sodium bicarbonate, to afford an optically pure arylamino alcohol (*e.g.*, structure **14**). Benzoxazine compounds (*e.g.*, structure **15**), may then be formed by cyclization of the *N*-alkyl substituted amino alcohol compounds (*e.g.*, structure **14)** by treatment with a base such as sodium hydride. Reduction of nitro benzoxazine compounds (*e.g.*, structure **15**) with a reducing agent, for example, zinc and calcium chloride affords an amino benzoxazine compound (*e.g.*, structure **16**). Treatment of an amino benzoxazine with a β-ketoester or its corresponding hydrate, for example ethyl 4,4,4-trifluoroacetoacetate, at

elevated temperatures, affords the corresponding acetanilide. Treatment of the acetanilide with an acid, for example, sulfuric acid, affords an optically pure quinolinone compound (*e.g.*, structures **17** and **18**). An enantiomer of structure **17**, or a racemic mixture may be obtained by the synthetic route as described in **Scheme III**, by starting with the enantiomer of the β-aminoalcohol as shown (*e.g.*, an (*S*)-β-amino alcohol), or a racemic mixture of the β-aminoalcohol shown (*e.g.*, a (±)-β-amino alcohol. Accordingly, an (*S*)-β-amino alcohol, employed in **Scheme III,** produces an (*S*)-quinolinone; an (*R*)-β-amino alcohol, employed in **Scheme III,** produces an (*R*)-quinolinone; and a racemic mixture of the β-amino alcohol, employed in **Scheme III,** produces a racemic mixture of the corresponding quinolinone.

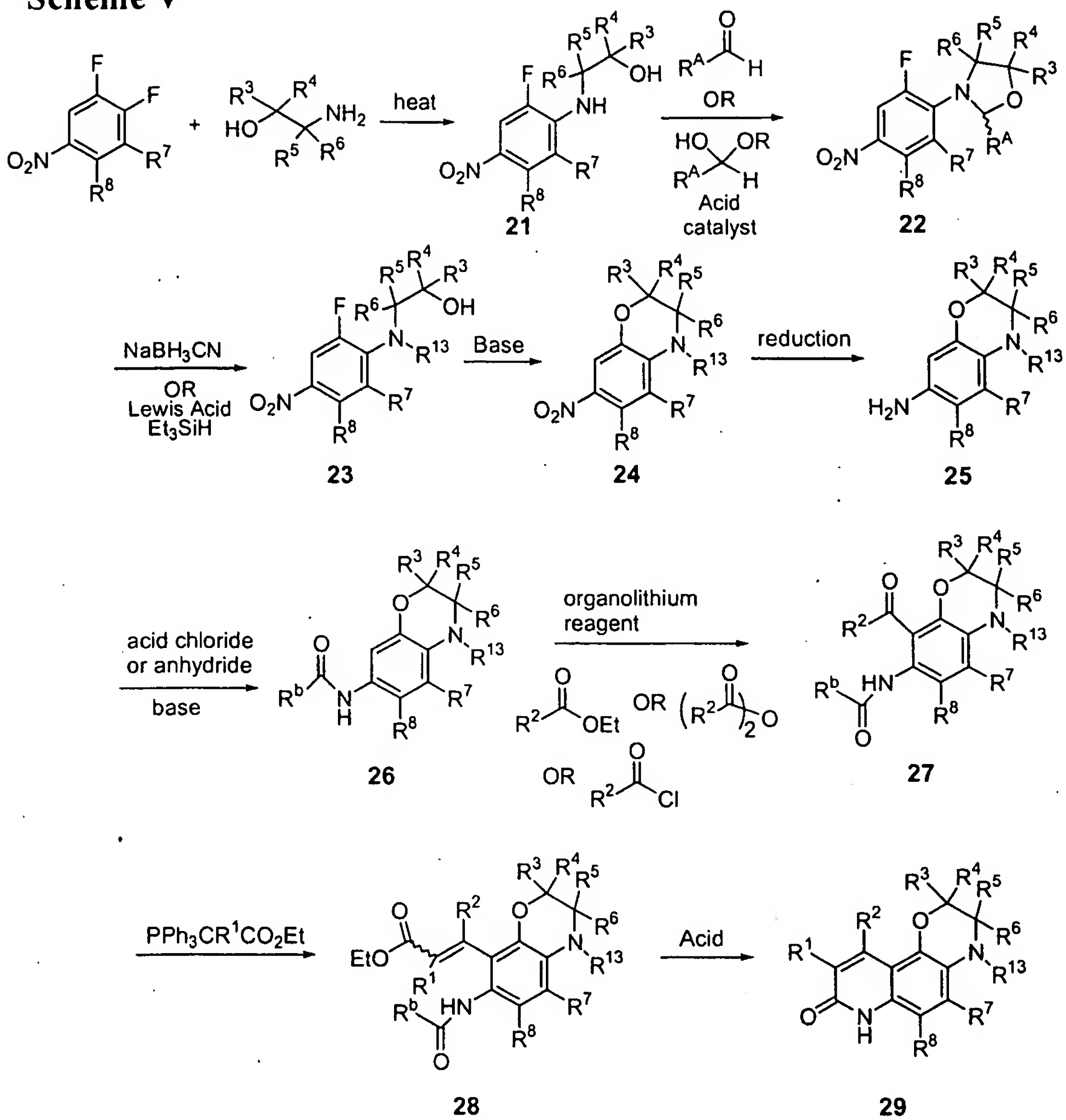
Scheme IV



11 **19** **20**

A synthesis of an 8*H*-[1,4]oxazino[2,3-f]quinoline (*e.g.*, structures **19** and **20**), is depicted in **Scheme IV**. The process of **Scheme IV** begins by treatment of a quinolinone with a halogenating agent, for example, phosphorus oxychloride, to afford a compound of structure **19**. Substitution of the halide can be accomplished by treatment with a nucleophile, for example, sodium methoxide in methanol, to afford a compound of structure **20**.

Scheme V

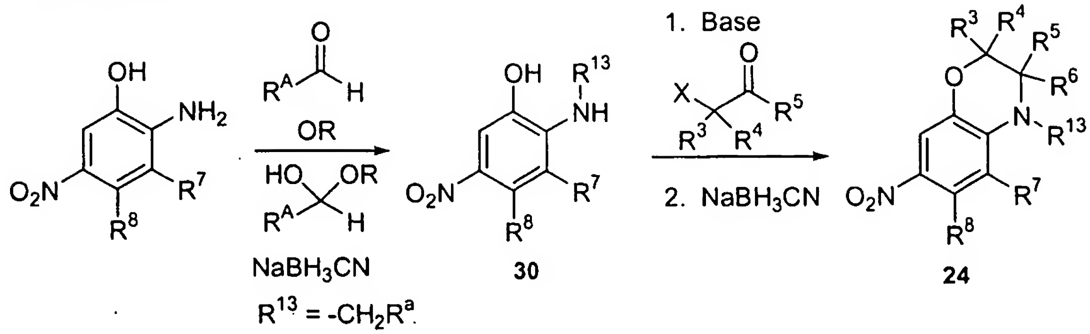


The asymmetric synthesis of **Scheme V** begins with the chemo- and regioselective *N*-alkylation of a β-aminoalcohol, either as a single enantiomer (*R* or *S*) or its racemate, for example, (*R*)-2-amino-1-butanol, onto a 3,4-dihalonitrobenzene, for example, 3,4-difluoronitrobenzene, to afford an optically pure arylamino alcohol (*e.g.*, Structure **21**). Treatment of amino alcohol compounds such as Structure **21** with an aldehyde or the corresponding hydrate or hemiacetal, for example, trifluoroacetaldehyde ethyl hemiacetal, in

the presence of an acid catalyst, for example p-toluenesulfonic acid, affords an optically pure oxazolidine compound (*e.g.*, structure **22**). Treatment of an oxazolidine compound such as structure **22** with a reducing agent, for example, triethylsilane, in the presence of an acid, for example, titanium tetrachloride, affords an *N*-alkyl substituted amino alcohol compound (*e.g.*, structure **23**). Benzoxazine compounds (*e.g.*, structure **24**), may then be formed by cyclization of the *N*-alkyl substituted amino alcohol compounds (*e.g.*, structure **23**) by treatment with a base such as sodium hydride. Reduction of nitro benzoxazine compounds (*e.g.*, structure **24**) with a reducing agent, for example, palladium on carbon under a hydrogen atmosphere, affords an aminobenzoxazine compound (*e.g.*, structure **25**). Treatment of a compound of structure **25** with an acylating agent, for example trimethylacetyl chloride, in the presence of a base, for example, pyridine, affords a compound of structure **26**. R^b may be, in addition to *t*-butyl, an aryl or a sterically hindered alkyl substituent. Alternatively, it may be t-butoxy, aryloxy, or a sterically hindered alkoxy substituent. Regioselective lithiation of a compound of structure **26** with a strong base, for example, *t*-butyllithium followed by quenching with an acylating agent, for example, ethyl trifluoroacetate, affords a compound of structure **27**. The base may be an alternative organolithium reagent, for example, *sec*-butyllithium or *n*-butyllithium. Treatment of a compound of structure **27** with a Horner-Emmons reagent, for example, (carbethoxymethylene)triphenylphosphorane produces a compound of structure **28**. Annulation of a compound of structure **28** to the pyridone ring may be accomplished by treatment of a compound of structure **28** with an acid, for example hydrochloric acid in acetic acid, to afford a compound of structure **29**.

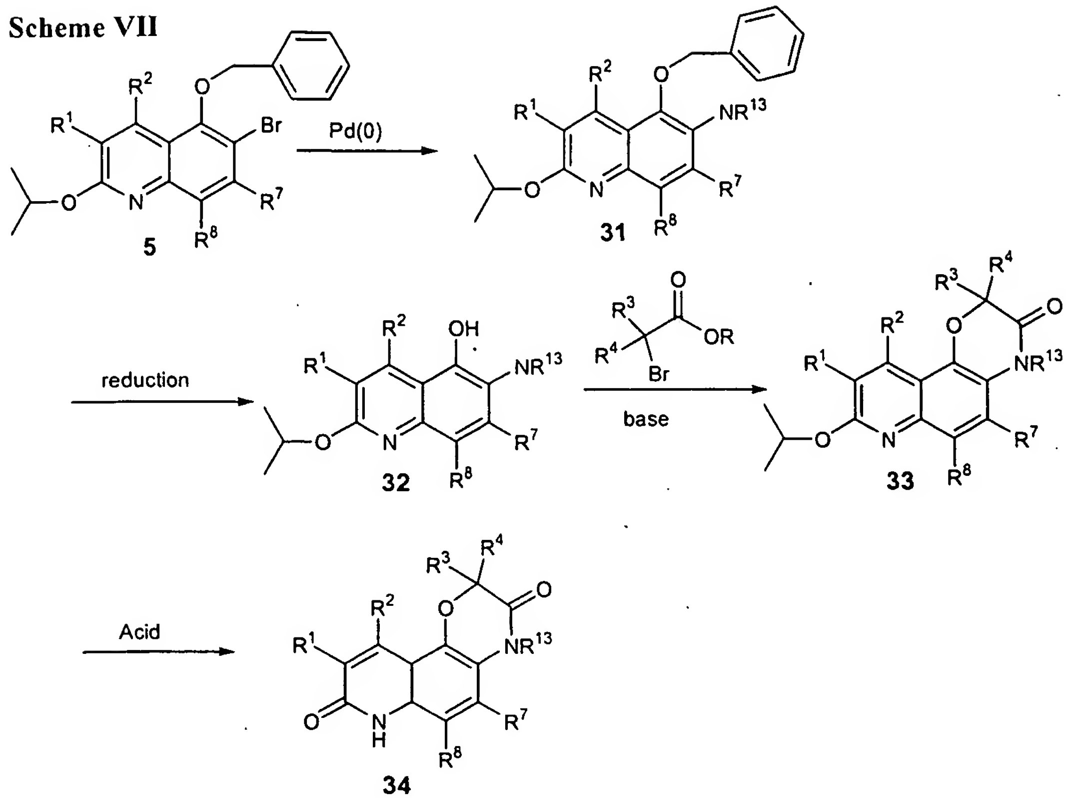
An enantiomer of structure **29**, or a racemic mixture, may be obtained by the synthetic route as described in **Scheme V**, by starting with the enantiomer of the β-aminoalcohol as shown (*e.g.*, an (*S*)-β-amino alcohol), or a racemic mixture of the β-aminoalcohol shown (*e.g.*, a (+)-β-amino alcohol. Accordingly, an (*S*)-β-amino alcohol, employed in **Scheme V**, produces an (*S*)-quinolinone; an (*R*)-β-amino alcohol, employed in **Scheme V**, produces an (*R*)-quinolinone; and a racemic mixture of the β-amino alcohol, employed in **Scheme V**, produces a racemic mixture of the corresponding quinolinone.

Scheme VI



An alternative racemic route to nitrobenzoxazine compounds of structure **24** (**Scheme VI**) begins with the *N*-alkylation of a 2-amino-5-nitrophenol nitrogen by treatment with an aldehyde, its corresponding hydrate or hemiacetal, with for example, trifluoroacetaldehyde hydrate in the presence of a reducing agent, for example, sodium cyanoborohydride, in an acid, for example trifluoroacetic acid. This procedure affords an *N*-alkylated compound of structure **30**. This can be further transformed by alkylation with a haloketone, for example, 2-bromobutanone, mediated by a base, for example, potassium carbonate, followed by treatment with a reducing agent, for example, sodium cyanoborohydride, in an acid, for example acetic acid, to afford a benzoxazine compound (*e.g.*, structure **24**).

Scheme VII



Scheme VII describes a route to compounds of structure **34**. A compound of structure **5** is treated with an amine, amide, or carbamate, for example butylamine, and a transition metal, for example $Pd_2(dba)_3$, in the presence of a ligand, for example BINAP, and a base, for example, cesium carbonate, to afford a compound of structure **31**. Removal of the benzyl group with a reducing agent, for example palladium on carbon under a hydrogen atmosphere, affords a compound of structure **32**. A compound of structure **32** is treated with an alpha-haloester, for example, ethyl bromoacetate, in the presence of a base, for example potassium carbonate, to afford a compound of structure **33**. A compound of structure **33** is hydrolyzed with an acid, for example, concentrated HCl in acetic acid, to afford a compound of structure **34**.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds.

Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, the steroid modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian and, more particularly, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired. Suitable administration routes include enteral (*e.g.*, oral), topical, suppository and parenteral (*e.g.*, intravenous, intramuscular and subcutaneous).

In preparing the compositions in oral liquid dosage forms (*e.g.*, suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (*e.g.*, powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be employed. Due to their ease of administration, tablets and capsules represent a desirable oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically include sterile water, although other ingredients that aid in solubility or serve as preservatives may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Examples of suitable cream bases are Nivea™, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Warner-Lambert (Morris Plains, New Jersey).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (*e.g.*, tablet, capsule, *etc.*). The compounds of the present invention generally are administered in a daily dosage of from about 1 μg/kg of body weight to about 500 mg/kg of body weight. Typically, the compounds of the present invention are administered in a daily dosage of from about 10 μg/kg to about 250 mg/kg of body weight. Most often, the compounds of the present invention are administered in a daily dosage of from about 20 μg/kg to about 100 mg/kg body weight. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient and the patient's tolerance for the drug.

The compounds of this invention also have utility when labeled (*e.g.*, radio-labeled, isotopically-labeled and the like) as ligands for use in assays to determine the presence of AR in a cell background or extract. They are particularly useful due to their ability to selectively activate androgen receptors and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors. Thus, the invention provides methods of determining the presence of androgen receptors (AR) in a cell or cell extract.

These invention methods comprise contacting the cell or cell extract with the compounds of the present invention which have been labeled and testing the contacted cell or cell extract to determine the presence of AR. Testing can be accomplished *via* testing for activation of androgen receptor(s) (*e.g.*, *via* elevated presence of the product of androgen mediated process(es)), *via* separation of the bound compound/receptor combination and the like, which techniques are known to those of skill in the art.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors

of choice and then isolating the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation and antibody complexing, among others. Thus, the invention also provides methods for purifying samples of steroid receptors *in vitro*. Invention methods comprise contacting a sample containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the steroid receptors to form a bound compound/receptor combination and separating out the bound compound/receptor combination.

The compounds and pharmaceutical compositions of the present invention can be used in the treatment of the diseases and conditions described herein. In this regard, the compounds and compositions of the present invention may prove particularly useful as modulators of male sex steroid-dependent diseases and conditions (*e.g.*, process(es) mediated by androgen receptors) such as the treatment of acne, male-pattern baldness, sexual dysfunction, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, impotence, cancer cachexia and various hormone-dependent cancers, including prostate and breast cancer. The compounds of the present invention may also prove useful in male hormone replacement therapy, stimulation of hematopoiesis, male contraception and as anabolic agents.

As utilized herein, the term "modulate" includes the ability of a modulator for a member of the androgen receptor family to either directly (by binding to the receptor as a ligand) or indirectly (as a precursor for a ligand or an inducer which promotes production of ligand from a precursor) induce expression of gene(s) maintained under hormone expression control, or to repress expression of gene(s) maintained under such control. Thus, both inhibitory effects on androgen receptors and activating effects on androgen receptors are contemplated within the scope of modulation.

The compounds of the present invention may be extremely potent activators of AR, displaying 50% maximal activation of AR (*e.g.*, activation of AR, determined by measurement of luciferase production levels compared to levels achieved by

dihydrotestosterone (DHT)) at a concentration of less than 100 nM (Cotransfection assay concentration), at a concentration of less than 50 nM, at a concentration of less than 20 nM, or even at a concentration of 10 nM or less. (See, for example, Biological Examples.)

In addition, selected compounds of the present invention may be extremely potent antagonists of AR, displaying 50% maximal inhibition of AR (*e.g.*, inhibition of AR, determined by measurement of luciferase production levels compared to levels achieved by dihydrotestosterone (DHT)) at a concentration of less than 100 nM (Cotransfection assay concentration), at a concentration of less than 50 nM, at a concentration of less than 20 nM, or even at a concentration of 10 nM or less. (See, for example, Biological Examples.)

Selective compounds of the present invention generally do not display undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR and AR, thereby limiting its use in long-term, chronic administration.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **101**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me)

5-Amino-7-chloro-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one: To a solution of 5-chloro-1,3-phenylenediamine (15.0 g, 0.105 mol) in 70 mL ethanol was added ethyl 4,4,4-trifluoroacetoacetate (20.4 g, 0.111 mol), then the mixture was heated at reflux for 18 h. The solvent was removed under reduced pressure until the product began to precipitate. The material was allowed to crystallize for 2 h, whereupon it was filtered and rinsed with cold ether to afford 10.9 g (37%) of 5-amino-7-chloro-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one, a tan solid. The filtrate was concentrated until solid began to precipitate

and afforded an additional 3.0 g (10%). ^{1}**H NMR** (400 MHz, acetone-d_6) δ 11.0 (broad s, 1H), 9.64 (s, 1H), 7.42 (t, 1H, *J* = 8.1), 6.99 (d, 1H, *J* = 8.1), 6.90 (s, 1H), 6.79 (d, 1H, *J* = 8.1).

5-Amino-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (Structure **2** of **Scheme I**, where R^1, R^7, R^8 = H, R^2 = trifluoromethyl): A mixture of 5-amino-7-chloro-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (8.0 g, 28 mmol), KOAc (5.6 g, 57 mmol) and 10% Pd-C (4.0 g) in 200 mL ethanol was stirred under an atmosphere of hydrogen for 2 h. The mixture was filtered through Celite and concentrated under reduced pressure. The resultant solid was dissolved in EtOAc (250 mL) and washed sequentially with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated to afford 7.0 g (100%) of 5-amino-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one, a foamy tan solid. ^{1}**H NMR** (400 MHz, acetone-d_6) δ 9.16 (broad s, 1H), 6.99 (t, 1H, *J* = 8.0), 6.44 (broad s, 1H), 6.39 (d, 1H, *J* = 7.9), 6.26 (d, 1H, *J* = 7.9), 5.44 (broad s, 2H), 3.09 (d, AB, *J* = 17.0), 2.93 (d, AB, *J* = 17.0).

5-Hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (Structure **3** of **Scheme I**, where R^1, R^7, R^8 = H, R^2 = trifluoromethyl): To a solution of 5-amino-3,4-dihydro-4-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (6.0 g, 24 mmol) in 100 mL 4.8 M H_2SO_4 was added a solution of $NaNO_2$ (1.85 g, 26.8 mmol) in 6 mL water at 0°C. The reaction mixture became deep red. This solution was transferred to 120 mL 10M H_2SO_4 preheated to 145°C. The mixture was heated at 145°C for 0.5 h, then poured into 400 g of ice water. The crude solid was adsorbed onto silica gel and eluted with 9:1 CH_2Cl_2:MeOH to afford 4.6 g (82%) of 5-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one, an off-white solid. ^{1}**H NMR** (400 MHz, acetone-d_6) δ 11.0 (broad s, 1H), 9.64 (s, 1H), 7.42 (t, 1H, *J* = 8.1), 6.99 (d, 1H, *J* = 8.1), 6.90 (s, 1H), 6.79 (d, 1H, *J* = 8.1).

6-Bromo-5-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (Structure **4** of **Scheme I**, where R^1, R^7, R^8 = H, R^2 = trifluoromethyl): To a solution of 5-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (4.38 g, 19.1 mmol) and diisopropylamine (14 mL, 100 mmol) in 100 mL EtOAc was added a solution of *N*-bromosuccinimide (3.74 g, 21.0 mmol) in 70 mL EtOAc at

−10°C over 30 min. The reaction mixture was stirred for 1 h, then acidified to pH 1 by the addition of 6M HCl. The mixture was extracted with EtOAc (3 x 150 mL) and the combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallization from chloroform:hexanes afforded 4.5 g (77%) of 6-bromo-5-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one, an off-white solid. R_f 0.4 (1:1 EtOAc:hexanes); ^{1}**H NMR** (400 MHz, acetone-d_6) δ 11.1 (broad s, 1H), 8.75 (broad s, 1H), 7.76 (d, 1H, J = 8.8), 7.04 (d, 1H, J = 8.8), 6.98 (s, 1H).

5-Benzyloxy-6-bromo-4-(trifluoromethyl)-1*H*-quinolin-2-one: To a suspension of 6-bromo-5-hydroxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (9.42 g, 30.6 mmol) and CsF (13.9 g, 91.7 mmol) in 102 mL DMF was added benzyl bromide (6.54 g, 38.2 mmol) dropwise. After 24 h, the mixture was poured into 0.1 M $NaHSO_4$ (500 mL) and extracted with EtOAc (1:1). The aqueous layer was reextracted with EtOAc (500 mL) and the combined organic layers were washed sequentially with water (500 mL), brine (300 mL), dried over $MgSO_4$, filtered and concentrated to a slurry. The mixture was cooled to 0°C, filtered and the resultant solids washed with cold EtOAc to afford 7.26 g (60%) of 5-benzyloxy-6-bromo-4-(trifluoromethyl)-1*H*-quinolin-2-one, a tan solid. R_f 0.26 (7:3 hexanes:acetone); ^{1}**H NMR** (400 MHz, acetone-d_6) δ 11.3 (broad s, 1H), 7.91 (d, 1H, J = 9.0, 1H), 7.61 (d, 2H, J = 7.3), 7.43 (t, 2H, J = 7.2), 7.25-7.35 (m, 1H), 7.32 (d, 1H, J = 9.0), 7.06 (s, 1H), 5.10 (s, 1H).

5-Benzyloxy-6-bromo-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **5** of **Scheme I**, where R^1, R^7, R^8 = H, R^2 = trifluoromethyl): To a suspension of 5-benzyloxy-6-bromo-4-(trifluoromethyl)-1*H*-quinolin-2-one (11.7 g, 29.4 mmol) and CsF (17.8 g, 117 mmol) in 150 mL DMF was added isopropyl iodide (19.9 g, 117 mmol). After 28 h, the mixture was partitioned between EtOAc (500 mL) and water (250 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water (200 mL), brine (100 mL), dried over $MgSO_4$, filtered and concentrated to afford 13 g (100%) of 5-benzyloxy-6-bromo-2-isopropoxy-4-(trifluoromethyl)quinoline. ^{1}**H NMR** (400 MHz,

$CDCl_3$) δ 7.85 (d, 1H, *J* = 9.0), 7.55-7.65 (m, 3H), 7.38-7.48 (m, 2H), 7.32-7.38 (m, 1H), 7.31 (s, 1H), 5.54 (sept, 1H, *J* = 6.2), 5.06 (s, 2H), 1.42 (d, 6H, *J* = 6.2).

6-Bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **6** of **Scheme I**, where R^1, R^7, R^8 = H, R^2 = trifluoromethyl): A solution of 5-benzyloxy-6-bromo-2-isopropoxy-4-(trifluoromethyl)quinoline (13.5 g, 30.8 mmol) in 31 mL methanesulfonic acid and 31 mL acetic acid was stirred at rt for 10 h, whereupon it was poured in water (500 mL), neutralized with K_2CO_3 (*ca.* 75 g) and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (2%-5% EtOAc:hexanes, gradient elution) afforded 9.9 g (92%) of 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline, a yellow-brown oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, 1H, *J* = 9.1), 7.38 (d, 1H, *J* = 9.1), 6.23 (s, 1H), 5.53 (sept, 1H, *J* = 6.2), 1.41 (d, 6H, *J* = 6.2).

General Method 1: Mitsunobu reaction of a phenol with a protected aminoalcohol. To a solution of the bromophenol substrate (1 equiv), the *N*-Boc-protected aminoalcohol (1.6 equiv), triphenylphosphine (1.6 equiv) and *N*-methylmorpholine (10 equiv) in dry THF (0.1-0.2 M) was added diisopropyl azodicarboxylate (1.6 equiv) dropwise, producing an orange color. After 5 min, the ice bath was removed and the reaction was stirred at rt for 2 – 16 h. The reaction mixture was poured into water (40 mL/mmol), neutralized with 1.0 M HCl and extracted with EtOAc (2 x 25 mL/mmol). The combined extracts were washed with of 0.1 M HCl (20 mL/mmol) and brine (20 mL/mmol), dried over $MgSO_4$, filtered, concentrated. Column chromatography (hexane:EtOAc) afforded the desired aryl ether.

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me): The compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.50 g, 1.43 mmol), (*R*)-*N*-Boc-alinol (400 mg, 2.28 mmol), triphenylphosphine (600 mg, 2.28 mmol) and diisopropyl azodicarboxylate (0.45 ml, 2.28 mmol) in 0.6 mL *N*-methylmorpholine in 14 mL dry THF to afford 484 mg (67%) of (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-

propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline after flash chromatography (100% hexanes to 6:1 hexanes/EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 9.3, 1H), 7.56 (d, *J* = 8.8, 1H), 7.30 (s, 1H), 5.53 (sept, *J* = 6.4, 1H), 4.95 (bs, 1H), 4.18 (m, 1H), 3.98 (m, 1H), 3.94 (m, 1H), 1.46 (s, 9H), 1.41 (d, *J* = 6.4, 6H), 1.37 (d, *J* = 6.8, 3H).

General Method 2: Hydrolysis of a *t*-butoxycarbonyl protected amine. To a solution of the carbamate substrate in CH_2Cl_2 (0.2 M) was added an equal volume of TFA and the solution was stirred at rt for 1 h. The mixture was poured into water (100 mL/mmol), neutralized with 6 M NaOH and extracted with EtOAc (2 x 50 mL/mmol). The combined extracts were washed sequentially with saturated $NaHCO_3$ (50 mL/mmol) and brine (50 mL/mmol), dried over $MgSO_4$, filtered and concentrated. Column chromatography (CH_2Cl_2/MeOH) afforded the desired free amine.

(*2'R*)-6-Bromo-5-(2'-amino-1'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline: This compound was prepared according to General Method 2 (EXAMPLE 1) from (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (480 mg, 0.95 mmol) in 5 mL CH_2Cl_2 and 5 mL TFA to afford 346 mg (90%) of (*2'R*)-6-bromo-5-(2'-amino-1'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8, 1H), 7.57 (d, J= 9.3, 1H), 7.30 (s, 1H), 5.53 (m, 1H), 3.93 (m, 1H) 3.84 (m, 1H), 3.66 (m, 1H), 2.33 (bs, 2H), 1.41 (d, *J* = 6.4, 3H), 1.40 (d, *J* = 6.4, 3H), 1.22 (d, *J* = 6.4, 3H).

General Method 3: Palladium catalyzed coupling of an amine with an aryl bromide. To a mixture of (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (4-10 mol %), $Pd_2(dba)_3$ (2-5 mol%), sodium *t*-butoxide (1.4 equiv) was added a solution of the amino aryl bromide (1 equiv) in toluene (0.1-0.2 M). The reddish solution was heated at 90-100°C for 6-24 h, whereupon it was poured into cold saturated NH_4Cl (20 mL/mmol). The mixture was extracted with EtOAc (2 x 40 mL/mmol) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes:EtOAc) afforded the desired 2*H*-[1,4]oxazino[2,3-*f*]quinoline.

(3*R*)-3,4-Dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me): This compound was prepared according to General Method 3 (EXAMPLE 1) from (2'*R*)-6-bromo-5-(2'-amino-1'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (346 mg, 0.85 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (21 mg, 4 mol%), $Pd_2(dba)_3$ (15.6 mg, 2 mol%), sodium *t*-butoxide (114 mg, 1.19 mmol) to afford 190 mg (70%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline after purification by flash chromatography (100% hexanes to 4:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.8, 1H), 7.18 (s, 1H), 7.03 (d, *J* = 8.8, 1H), 5.47 (m, 1H), 4.33 (dd, *J* = 10.7, 2.9, 1H), 3.78 (dd, *J* = 10.7, 8.1, 1H), 3.74 (bs, 1H), 3.66 (m, 1H), 1.38 (d, *J* = 5.9, 3H), 1.37 (d, *J* = 6.4, 3H), 1.24 (d, *J* = 6.4, 3H).

General Method 4: Acid mediated hydrolysis of an isopropyl imino ether to a pyridone. A solution of the imino ether in a 3:1 acetic acid:concentrated HCl (0.1-0.2 M) solution was heated 60-100°C for 4-16 h. The solution was poured into saturated $NaHCO_3$ (80 mL/mmol), extracted with EtOAc (2 x 80 mL), dried over $MgSO_4$, filtered and concentrated and purified as indicated.

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **101**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me): Compound **101** was prepared by General Method 4 (EXAMPLE 1) from (*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (14 mg, 0.043 mmol) in 1:1 acetic acid:concentrated HCl (0.01M) heated at 90°C for 4 h to afford 7 mg (58%) of Compound **101**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 12.37 (bs, 1H), 7.13 (s, 1H), 6.94 (d, *J* = 8.79, 1H), 6.92 (d, *J* = 8.79, 1H), 4.34 (dd, *J* = 10.74, 2.93, 1H), 3.79 (dd, *J* = 10.74, 8.10, 1H), 3.69 (bs, 1H), 3.62 (m, 1H), 1.24 (d, *J* = 6.35, 3H).

EXAMPLE 2

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **102**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = CH_3)

General Method 5: Reductive amination of a 2*H*-[1,4]oxazino[2,3-*f*]quinoline or an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one derivative with sodium cyanoborohydride and an aldehyde, its hydrate, or its hemiacetal. A solution of the 2*H*-[1,4]oxazino[2,3-*f*]quinoline or 8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (1 equiv) and the aldehyde, its hydrate or hemiacetal (10 equiv) in acetic acid or trifluoroacetic acid, was stirred at room temperature for 2 h, whereupon sodium cyanoborohydride (5 equiv) was added portionwise. The solution was stirred for 12-24 h at rt, then poured into cold saturated $NaHCO_3$ (pH 8-10). The aqueous layer was extracted with EtOAc (2 x 40 mL/mmol) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and purified as indicated, or used directly in the next step.

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **102**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = CH_3): Compound **102** was prepared according to General Method 5 (EXAMPLE 2) from (3*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (12 mg, 0.04 mmol), 37% formaldehyde solution (0.010 mL, 0.2 mmol, 5 equiv) and $NaCNBH_3$ (10 mg, 0.2 mmol, 5 equiv) in 1 mL AcOH (0.04 M) to afford 9 mg (*ca.* 70%) of (*R*)-3,4-dihydro-8-isopropoxy-3,4-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (9 mg, 0.03 mmol) was taken on directly according to General Method 4 (EXAMPLE 1) by treatment with 3 mL acetic acid and 3 mL concentrated HCl and heated at 90°C for 4 h to afford 7 mg (89%) of Compound **102** after flash chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.90 (bs, 1H), 7.12 (s, 1H), 7.01 (d, *J* = 9.3, 1H), 6.96 (d, *J* = 9.3, 1H), 4.19 (dd, *J* = 10.7, 2.9, 1H), 4.11 (dd, *J* = 10.7, 3.7, 1H), 3.43 (m, 1H), 2.93 (s, 3H), 1.21 (d, *J* = 6.8, 3H)

EXAMPLE 3

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **103**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = CH_2CH_3)

General Method 6: Reductive amination of a 2*H*-[1,4]oxazino[2,3-*f*]quinoline or an 8*H*-[1,4]oxazino[2,3-*f*]quinolin-2-one with sodium borohydride with acetic acid or a substituted acetic acid. To a solution of the 2*H*-[1,4]oxazino[2,3-*f*]quinoline or 8*H*-[1,4]oxazino[2,3-*f*]quinolin-2-one in a substituted acetic acid was added $NaBH_4$ pellets (5-10 equiv). After 12-24 h, the reaction was carefully poured into cold saturated $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 x 40 mL/mmol) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated and the compound was purified as indicated.

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **103**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = CH_2CH_3): This compound was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (16 mg, 0.049 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 5 mL acetic acid (0.01 M stirred at rt for 12 h, to afford 18 mg (100%) of (3*R*)-4-ethyl-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (18 mg, 0.050 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 2.5 mL acetic acid and 2.5 mL concentrated HCl and heated at 90°C for 4 h to afford 9 mg (57%) of Compound **103**, after purification by column chromatography (3:1 hexanes: EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.02 (bs, 1H), 7.12 (s, 1H), 7.04 (d, J = 8.8, 1H), 6.97 (d, J = 9.3, 1H), 4.10 (dd, J = 10.2, 3.4, 1H), 4.02 (dd, J = 10.3, 2.9, 1H), 3.53 (m, 1H), 3.43 (m, 1H), 3.32 (m, 1H), 1.22 (d, J = 6.9, 3H), 1.18 (t, J = 7.1, 3H).

EXAMPLE 4

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **104**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = CH_2CF_3)

This compound was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (4 mg, 0.01 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 2.5 mL trifluoroacetic acid (0.005 M) stirred at rt for 12 h, to afford 4 mg (80%) of (*R*)-3,4-dihydro-8-isopropoxy-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (4 mg, 0.01 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 2 mL acetic acid and 2 mL concentrated HCl (0.003 M) and heated at 90°C for 4 h to afford 3.2 mg (71%) of Compound **104**, after purification by column chromatography (3:1 hexanes: EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.00 (bs, 1H), 7.16 (s, 1H), 7.11 (d, *J* = 9.3, 1H), 7.00 (d, *J* = 8.8, 1H), 4.20 (d, *J* = 10.7, 2.9, 1H), 4.09 (dd, *J* = 10.7, 2.4, 1H), 3.82 (m, 2H), 3.60 (m, 1H), 1.26 (d, *J* = 6.8, 3H).

EXAMPLE 5

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **105**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = $CH_2CH_2CH_3$)

This compound was prepared according General Method 6 (EXAMPLE 3) from (3*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (11 mg, 0.03 mmol), propionaldehyde (0.3 mmol, 10 eq) and $NaCNBH_3$ (10 equiv) in 4 mL TFA (0.03 M) stirred at rt for 12 h to afford 12 mg (100%) of (*R*)-3,4-dihydro-8-isopropoxy-3-methyl-4-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (12 mg, 0.030 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 3 mL acetic acid and 3 mL concentrated HCl and heated at 90°C for 4 h to

afford 8 mg (75%) of Compound **105** after purification by silica gel chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.15 (bs, 1H), 7.10 (s, 1H), 6.99 (d, J = 8.8, 1H), 6.88 (d, J = 8.8, 1H), 4.11 (dd, J = 10.7, 3.2, 1H), 4.03 (dd, J = 10.7, 2.4, 1H), 3.51 (m, 1H), 3.30 (m, 1H), 3.14 (m, 1H), 1.64 (m, 2H), 1.21 (d, J = 6.4, 3H), 0.97 (t, J = 7.3, 3H).

EXAMPLE 6

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **106**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Me, R^{13} = $-CH_2CH{=}CH_2$)

To a suspension of (*R*)-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (13 mg, 0.04 mmol) and K_2CO_3 (28 mg, 0.2 mmol, 5 eq) in 1 ml DMF (0.04 M) was added allylbromide (0.03 mL, 0.4 mmol, 10 eq). The reaction was heated to 50°C and allowed to stir for 12 h, whereupon the reaction was poured into 10 mL water and neutralized with 1N HCl. The aqueous layer was extracted with EtOAc (2 x 40 mL/mmol) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated to afford 10 mg (75%) of (*R*)-4-allyl-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (10 mg, 0.03 mmol) was carried on directly according to General Method 4 (EXAMPLE 1) by treatment with 2 mL concentrated HCl (0.01M) and heated at 50°C for 6 h to afford 6 mg (67%) of Compound **106** after silica gel column chromatography (gradient 3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution) ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.89 (bs, 1H), 7.11 (s, 1H), 7.00 (d, J = 8.8, 1H), 6.93 (d, J = 8.8, 1H), 5.86 (m, 1H), 5.24 (m, 2H), 4.10 (m, 2H), 3.90 (m, 2H), 3.55 (m, 1H), 1.22 (d, J = 6.8, 3H).

EXAMPLE 7

<u>(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **107**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et)</u>

<u>(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et)</u>: This compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (1.5 g, 4.4 mmol), (2*R*)-2-*N*-*t*-butoxycarbonylamino-1-butanol (1.5 g, 7.8 mmol), triphenylphosphine (2.0 g, 7.8 mmol), DIAD (1.5 mL, 7.8 mmol) and *N*-methylmorpholine (2.0 mL) in THF (40 mL) to afford 1.7 g (74%) of 6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline as a tan solid. R_f 0.4 (9:1 hexane:EtOAc); [1]**H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, 1H, *J* = 8.9), 7.55 (d, 1H, *J* = 8.9), 7.29 (s, 1H), 5.52 (septet, 1H, *J* = 6.3), 4.80 (broad s, 1H), 4.06-3.90 (m, 3H), 1.91-1.81 (m, 1H), 1.71-1.59 (m, 1H), 1.46 (s, 9H), 1.41 (d, 6H, *J* = 6.2), 1.01 (t, 3H, *J* = 7.4).

<u>(3*R*)-3-Ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et)</u>: This compound was prepared according to General Method 2 (EXAMPLE 1) from 6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (1.3 g, 2.5 mmol) in CH_2Cl_2 (10 mL) and TFA (10 mL) to afford 1.0 g (95%) of (2'*R*)-6-bromo-5-(2'-amino-1'-butoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline. This material (1.0 g, 2.4 mmol) was carried on according to General Method 3 (EXAMPLE 1) by treatment with $Pd_2(dba)_3$ (0.043 g, 2 mol%), BINAP (0.059 g, 4 mol%) and *t*-BuONa (0.32 g, 3.3 mmol) in toluene (10 mL) heated at reflux to afford 0.51 g (63%) of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid. R_f 0.4 (9:1 hexane:EtOAc); [1]**H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, 1H, *J* = 8.8), 7.18 (s, 1H), 7.03 (d, 1H, *J* = 8.8), 5.47 (septet, 1H, *J* = 6.2), 4.36 (dd, *ABX*, 1H, *J* = 10.6, 2.9), 3.87 (dd, *ABX*, 1H,

J = 10.4, 7.5), 3.83 (broad s, 1H), 3.48-3.40 (m, 1H), 1.63-1.53 (m, 2H), 1.38 (d, 6H, J = 6.2), 1.06 (t, 3H, J = 7.4).

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **107**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et): Compound **107** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.220 g, 0.646 mmol) in conc. HCl (1.0 mL) in AcOH (2.0 mL) heated at 90°C to afford 0.190 g (98%) of Compound **107**, a yellow solid. R_f 0.4 (9:1 CH_2Cl_2;MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.63 (broad s, 1H), 7.12 (s, 1H), 6.96 (d, 1H, J = 8.6), 6.92 (d, 1H, J = 8.6), 4.36 (dd, *ABX*, 1H, J = 10.3, 2.8), 3.86 (dd, *ABX*, 1H, J = 10.6, 7.8), 3.77 (broad s, 1H), 3.43-3.33 (m, 1H), 1.62-1.50 (m, 2H), 1.05 (t, 3H, J = 7.5).

EXAMPLE 8

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **108**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_3)

(3*R*)-3-Ethyl-3,4-dihydro-8-isopropoxy-4-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_3): This compound was prepared by General Method 5 (EXAMPLE 1) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.015 g, 0.044 mmol), paraformaldehyde (0.013 g, 0.44 mmol) and $NaCNBH_3$ (0.014 g, 0.22 mmol) in 1 mL glacial acetic acid to afford 0.014 g (93%) of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, of sufficient purity as to be used directly in the next reaction. R_f 0.5 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 9.0), 7.20 (d, 1H, J = 9.0), 7.18 (s, 1H), 5.48 (septet, 1H, J = 6.2), 4.29 (dd, *ABX*, 1H, J = 10.7, 2.5), 4.02 (dd, *ABX*, 1H, J = 10.7, 2.7), 3.21-3.16 (m, 1H), 3.03 (s, 3H), 1.74-1.56 (m, 2H), 1.39 (d, 3H, J = 6.2), 1.37 (d, 3H, J = 6.2), 0.99 (t, 3H, J = 7.5).

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **108**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_3): Compound **108** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.014 g, 0.039 mmol) in conc. HCl (0.5 mL) in AcOH (1.0 mL) heated at 90°C to afford 10 mg (83%) of Compound **108,** a yellow solid. R_f 0.6 (9:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.53 (broad s, 1H), 7.13 (s, 1H), 7.01 (s, 2H), 4.29 (dd, *ABX*, 1H, *J* = 10.7, 2.5), 4.05 (dd, *ABX*, 1H, *J* = 10.7, 2.7), 3.20-3.14 (m, 1H), 2.98 (s, 3H), 1.74-1.52 (m, 2H), 0.98 (t, 3H, *J* = 7.5).

EXAMPLE 9

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **109**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CH_3)

(3*R*)-3,4-Diethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CH_3): A solution of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.020 g, 0.059 mmol), excess acetic anhydride (*ca.* 0.5 mL) and excess triethylamine (*ca.* 0.5 mL) in THF was heated at 50°C for 24 h. The reaction mixture was poured into 25 mL water and extracted with EtOAc (2 x 25 mL). The extracts were washed sequentially with 25 mL portions of saturated $NaHCO_3$, 0.1 N HCl and brine, dried over $MgSO_4$, filtered and concentrated to afford 0.018 g of a yellow oil. This crude material was dissolved in 1.5 mL MTBE, transferred to a slurry of LAH (0.003 g) in 1.5 mL MTBE and heated to reflux for 20 h. The reaction mixture was poured into water (25 mL) and extracted with diethyl ether (2 x 25 mL). The extracts were washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated to 0.013 g yellow oil. Column chromatography (5-10% EtOAc in hexane gradient) afforded 4 mg (18%) of (3*R*)-3,4-diethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline

as a yellow oil. R_f 0.7 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.43 (d, 1H, J = 9.0), 7.26 (d, 1H, J = 9.0), 7.17 (s, 1H), 5.47 (septet, 1H, J = 6.2), 4.30 (dd, *ABX*, 1H, J = 10.4, 2.1), 3.83 (dd, *ABX*, 1H, J = 10.5, 2.6), 3.56-3.48 (m, 1H), 3.37-3.28 (m, 1H), 3.25-3.19 (m, 1H), 1.65-1.55 (m, 2H), 1.39 (d, 3H, J = 6.2), 1.37 (d, 3H, J = 6.2), 1.20 (t, 3H, J = 7.1), 0.98 (t, 3H, J = 7.4).

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **109**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CH_3): Compound **109** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-diethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.008 g, 0.022 mmol) in conc. HCl (0.5 mL) and AcOH (1.0 mL) heated at 90°C to afford 6 mg (86%) of Compound **109**, a yellow solid. R_f 0.6 (9:1 CH_2Cl_2;MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.43 (broad s, 1H), 7.13 (s, 1H), 7.08 (d, 1H, J = 9.0),), 7.01 (d, 1H, J = 9.0), 4.29 (dd, *ABX*, 1H, J = 10.5, 1.9), 3.85 (dd, *ABX*, 1H, J = 10.6, 2.6), 3.50-3.41 (m, 1H), 3.32-3.23 (m, 1H), 3.25-3.16 (m, 1H), 1.65-1.51 (m, 2H), 1.18 (t, 3H, J = 7.1), 0.97 (t, 3H, J = 7.5).

EXAMPLE 10

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **110**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CF_3)

This compound was prepared according to General Method 5 (EXAMPLE 2) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.008 g, 0.024 mmol), $NaCNBH_3$ (0.007 g, 0.118 mmol) and trifluoroacetaldehyde ethyl hemiacetal (0.028 mL, 0.235 mmol) in TFA (0.8 mL) to afford 0.017 g of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a brown-red solid. This material (0.017g) was carried on according to General Method 4 (EXAMPLE 1) by treatment with conc. HCl (0.3 mL) in AcOH (0.6 mL) and heated at 95°C for 2 h to afford 0.006 g (67% for the 2 steps) of Compound **110**, a yellow

solid: R_f 0.4 (9:1 CH_2Cl_2:MeOH); ^{1}**H** NMR (400 MHz, $CDCl_3$) δ 12.47 (broad s, 1H), 7.15 (s, 1H), 7.14 (d, 1H, *J* = 8.9), 7.02 (d, 1H, *J* = 8.9), 4.38 (d, 1H, *J* = 10.9), 3.98 (dd, 1H, *J* = 10.8, 2.4) 3.93-3.65 (m, 2H), 3.27-3.22 (m, 1H), 1.68-1.51(m, 2H), 0.98 (t, 3H, *J* = 7.5).

EXAMPLE 11

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **111**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CClF_2)

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CClF_2): This compound was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (22 mg, 0.06 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 4 mL chlorodifluoroacetic acid (0.02 M) stirred at rt for 12 h, to afford 17 mg (61%) of (3*R*)-4-(2-chloro-2,2-difluoroethyl)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. ^{1}**H NMR** (500 MHz, $CDCl_3$) 7.44 (d, 1H, J = 9.3), 7.32 (d, J = 1 H, 9.3), 7.21 (s, 1H), 5.50 (m, 1H), 4.39 (dd, 1H, J = 10.7, 1.5), 4.09 (m, 1H), 3.99 (dd, 1H, J = 10.7, 2.4), 3.92 (m, 1H), 3.33 (m, 1H), 1.6 (m, 2H), 1.39 (d, 3H, J = 6.3), 1.38 (d, 3H, J = 6.3), 0.99 (t, 3H, J = 7.3).

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **111**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CClF_2): Compound **111** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-4-(2-chloro-2,2-difluoroethyl)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (17 mg. 0.03 mmol) in 1 mL acetic acid and 1 mL concentrated HCl heated at 90°C for 4 h to afford 8 mg (53%) of Compound **111**, after purification by flash chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) 12.54 (bs, 1H), 7.19 (d, 1H, J = 8.8), 7.15 (s, 1H), 7.03 (d, 1H, J = 8.8), 4.39 (d,

1H, J = 10.7), 4.06 (m, 1H), 4.01 (dd, 1H, J = 10.3, 2.0), 3.86 (m, 1H), 3.31 (m, 1H), 1.59 (m, 2H), 0.98 (t, 3H, J = 7.3).

EXAMPLE 12

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **112**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CHF_2)

Compound **112** was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (13 mg, 0.04 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 3 mL difluoroacetic acid (0.01 M) stirred at rt for 12 h, to afford 8 mg (53%) of (3*R*)-4-(2,2-difluoroethyl)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (8 mg, 0.02 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 1.5 mL acetic acid and 1.5 mL concentrated HCl and heated at 90°C for 4 h to afford 4 mg (57 %) of Compound **112**, after purification by column chromatography (3:1 hexanes: EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) 12.19 (bs, 1H), 7.14 (s, 1H), 7.09 (d, 1H, J = 8.8), 6.99 (d, 1H, J = 9.3), 5.95 (m, 1H), 4.34 (dd, 1H, J = 10.7, 1.5), 3.98 (dd, 1H, J = 10.7, 2.4), 3.70 (m, 1H), 3.58 (m, 1H), 3.25 (m, 1H), 1.58 (m, 2H), 0.98 (t, 3H, J = 7.3).

EXAMPLE 13

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **113**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = $CH_2CH_2CH_3$)

(3*R*)-4-Allyl-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline:. To a suspension of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.250 g, 0.734 mmol) and K_2CO_3 (0.507 g, 3.67 mmol) in 3 mL DMF was added allyl bromide (0.636 mL, 7.34 mmol) and the reaction mixture was heated to 50°C for 4 h. The reaction mixture was poured into 40 mL

water and extracted with EtOAc (2 x 30 mL). The extracts were washed with 40 mL each water and brine, dried over $MgSO_4$, filtered and concentrated to a yellow oil. Column chromatography (5-10 % EtOAc in hexane gradient) afforded 0.24 g (86% yield) of (3*R*)-4-allyl-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. R_f 0.6 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, 1H, *J* = 9.0), 7.21 (d, 1H, *J* = 9.0), 7.18 (s, 1H), 5.96-5.85 (m, 1H), 5.47 (septet, 1H, *J* = 6.1), 5.25 (dd, *ABX*, 1H, *J* = 17.1, 1.1), 5.20 (d, 1H, *J* = 10.1), 4.31 (dd, *ABX*, 1H, *J* = 10.7, 2.2), 4.03 (dd, *ABX*, 1H, *J* = 16.8, 5.0), 3.95-3.89 (m, 2H), 3.27-3.22 (m, 1H), 1.69-1.59 (m, 2H), 1.38 (d, 3H, *J* = 6.1), 1.37 (d, 3H, *J* = 6.1), 0.97 (t, 3H, *J* = 7.5).

<u>(3*R*)-3-Ethyl-3,4-dihydro-8-isopropoxy-4-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline</u>: To a solution of (3*R*)-4-allyl-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.24 g, 0.63 mmol) and 0.1 mL Et_3N in 3 mL EtOAc was added 10% Pd on carbon (0.08 g) and the mixture was vigorously stirred under H_2 atmosphere for 1 h. The reaction mixture was filtered through Celite and concentrated to give 0.23 g (96% yield) of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. R_f 0.7 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, 1H, *J* = 9.1), 7.22 (d, 1H, *J* = 9.1), 7.17 (s, 1H), 5.47 (septet, 1H, *J* = 6.2), 4.30 (dd, *ABX*, 1H, *J* = 10.5, 1.6), 3.86 (dd, *ABX*, 1H, *J* = 10.5, 2.5), 3.47-3.35 (m, 1H), 3.23-3.11 (m, 2H), 1.70-1.55 (m, 4H), 1.38 (d, 3H, *J* = 6.2), 1.37 (d, 3H, *J* = 6.2), 1.02-0.91 (m, 6H).

<u>(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **113**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = $CH_2CH_2CH_3$)</u>: Compound **113** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.23 g, 0.60 mmol) in conc. HCl (2.0 mL) and AcOH (4.0 mL) heated at 95°C to afford 0.18 g (88%) of Compound **113,** a yellow solid. R_f 0.6 (9:1 CH_2Cl_2;MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.79 (broad s, 1H), 7.11 (s, 1H), 7.03 (d, 1H, *J* = 8.9),), 6.93 (d, 1H, *J* = 8.8), 4.30 (dd, *ABX*, 1H, *J* = 10.8, 2.0), 3.89 (dd, *ABX*,

1H, $J = 10.6, 2.7$), 3.39-3.29 (m, 1H), 3.21-3.16 (m, 1H), 3.16-3.06 (m, 1H), 1.69-1.51 (m, 4H), 1.01-0.93 (m, 6H).

EXAMPLE 14

(3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **114**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = $-CH_2CH{=}CH_2$)

Compound **114** was prepared by General Method 4 (EXAMPLE 1) from (3*R*)-4-allyl-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (EXAMPLE 13) (0.016 g, 0.041 mmol) in conc. HCl (1 mL) heated at 75°C to afford 13 mg (93%) of Compound **114**, a yellow solid. R_f 0.5 (9:1 CH_2Cl_2;MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.52 (broad s, 1H), 7.12 (s, 1H), 7.04 (d, 1H, $J = 8.9$), 6.99 (d, 1H, $J = 8.9$), 5.91-5.81 (m, 1H), 5.26-5.18 (m, 2H), 4.31 (dd, *ABX*, 1H, $J = 10.6, 2.2$), 4.00-3.92 (m, 2H), 3.87 (dd, *ABX*, 1H, $J = 16.8, 5.1$), 3.25-3.20 (m, 1H), 1.65-1.51 (m, 2H), 0.96 (t, 3H, $J = 7.4$).

EXAMPLE 15

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **115**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = $CH_2CH(CH_3)_2$)

(3*R*)-3-Ethyl-3,4-dihydro-8-isopropoxy-4-methallyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline: To a suspension of (*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.020 g, 0.059 mmol) and K_2CO_3 (0.041 g, 0.295 mmol) in 1 mL DMF was added methallyl bromide (0.077 mL, 0.767 mmol) and the reaction mixture was heated to 50°C for 16 h. The reaction mixture was poured into 25 mL water and extracted with EtOAc (2 x 25 mL). The extracts were washed with 25 mL each water and brine, dried over $MgSO_4$, filtered and concentrated to a yellow oil. Column chromatography (5-10% EtOAc in hexane gradient) gave 0.020 g (87%) of (*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-methallyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a

yellow oil. R_f 0.7 (9:1 hexane:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, 1H, *J* = 9.0), 7.18 (s, 1H), 7.12 (d, 1H, *J* = 9.0), 5.47 (septet, 1H, *J* = 6.2), 4.91 (s, 2H), 4.33 (dd, *ABX*, 1H, *J* = 10.6, 2.0), 3.96 (dd, *ABX*, 1H, *J* = 10.7, 2.6), 3.86 (d, 1H, *J* = 17.0), 3.80 (d, 1H, *J* = 17.0), 3.25-3.20 (m, 1H), 1.79 (s, 3H), 1.65-1.59 (m, 2H), 1.38 (d, 3H, *J* = 6.1), 1.37 (d, 3H, *J* = 6.1), 0.97 (t, 3H, *J* = 7.5).

<u>(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **115**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = $CH_2CH(CH_3)_2$)</u>: To a solution of (*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-4-methallyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.010 g, 0.025 mmol in 1.5 mL EtOAc and 0.1 mL Et_3N was added 10% Pd on carbon (0.006 g) and the mixture was vigorously stirred under H_2 atmosphere for 1 h. The reaction mixture was filtered through Celite and concentrated to afford 0.010 g (100% yield) of (*R*)-3-ethyl-3,4-dihydro-4-isobutyl-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. This material (0.010 g, 0.025 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with conc. HCl (0.5 mL) in AcOH (1.0 mL) and heated at 95°C to afford Compound **115** (0.008 g, 89% yield) as a yellow solid. R_f 0.5 (9:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.81 (broad s, 1H), 7.11 (s, 1H), 7.00 (d, 1H, *J* = 9.0), 6.92 (d, 1H, *J* = 9.0), 4.33 (dd, *ABX*, 1H, *J* = 10.4, 1.2), 3.98 (dd, *ABX*, 1H, *J* = 10.4, 2.3), 3.23 (dd, *ABX*, 1H, *J* = 14.5, 4.8), 3.15-3.10 (m, 1H), 2.80 (dd, *ABX*, 1H, *J* = 14.5, 9.8), 2.07-1.97 (m, 1H), 1.62-1.49 (m, 2H), 1.01 (d, 3H, *J* = 6.5), 0.98-0.92 (m, 6H).

<u>EXAMPLE 16</u>

<u>(±)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **116**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = *n*-Pr)</u>

<u>(±)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = *n*-Pr)</u>: This compounds was prepared according to General Method 1

(EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.5 g, 1.43 mmol, 1 equiv), (±)-2-(*N*-*t*-butoxycarbonylamino)-1-pentanol (470 mg, 2.28 mol, 1.6 equiv), triphenylphosphine (600 mg, 2.28 mol, 1.6 equiv), diisopropyl azodicarboxylate (0.45 ml, 2.28 mol, 1.6 equiv) and *N*-methylmorpholine (0.6 ml, 10 equiv) in dry THF (14 ml, 0.1 M) to afford 483 mg (63%) of (±)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline, a white foam, after column chromatography (100% hexanes to 9:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.8 (d, J = 8.8, 1H), 7.55 (d, J = 8.8, 1H), 7.3 (s, 1H), 5.52 (m, 1H), 4.79 (bs, 1H), 4.12 (m, 1H), 3.99 (m, 2H), 1.7 (m, 1H), 1.63 (m, 1H), 1.46 (s, 9H), 1.41 (d, J = 5.9, 6H), 0.98 (t, J = 7.3, 3H).

(±)-6-Bromo-5-(2'-amino-1'-pentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline: This compound was prepared according to General Method 2 (EXAMPLE 1) from (±)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (480 mg, 0.9 mmol) in 5 mL CH_2Cl_2 and 5 mL TFA (0.09 M) stirred at rt for 2 h to afford 280 mg (72%) of (±)-6-bromo-5-(2'-amino-1'-pentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline after column chromatography (9:1 hexanes:ethyl acetate to 1:1 hexanes:ethyl acetate, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.8, 1H), 7.55 (d, J = 8.8, 1H), 7.30 (s, 1H), 5.53 (m, 1H), 3.86 (m, 2H), 3.45 (m, 1H), 1.42 (d, J = 5.9, 3H), 1.41 (d, J = 5.9, 3H), 1.39 (m, 4H), 0.95 (t, J = 6.8, 3H).

(±)-3,4-Dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *n*-Pr): This compound was prepared according to General Method 3 (EXAMPLE 1) from (±)-6-bromo-5-(2'-amino-1'-pentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (280 mg, 0.64 mol, 1 equiv), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (16 mg, 4 mol %), $Pd_2(dba)_3$ (11.8 mg, 2 mol%), sodium *t*-butoxide (87 mg, 0.9 mmol, 1.4 equiv) in 5 mL toluene (0.2 M) heated at 90°C for 12 h to afford 172 mg (75%) of (±)-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline after flash chromatography (100% hexanes to 4:1 hexanes:EtOAc). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.36 (d, J = 8.8, 1H), 7.18 (s, 1H),

7.03 (d, J = 8.8, 1H), 5.47 (m, 1H), 4.35 (dd, J = 10.7, 2.9, 1H), 3.85 (dd, J = 10.7, 7.6, 1H), 3.81 (s, 1H), 3.52 (m, 1H), 1.51 (m, 4H), 1.38 (d, J = 5.9, 6H), 1.00 (t, J = 6.6, 3H).

<u>(±)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **116**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *n*-Pr)</u>: Compound **116** was prepared according to General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (10 mg, 0.03 mmol) in 1 mL 1:1 acetic acid:concentrated HCl (0.03 M) heated at 90°C for 3 h to afford 8 mg (97%) of Compound **116**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.55 (bs, 1H), 7.11 (s, 1H), 6.91 (d, J = 8.8, 1H), 6.86 (d, J = 8.8, 1H), 4.35 (dd, J = 10.25, 2.93, 1H), 3.85 (dd, J = 10.7, 7.8, 1H), 3.73 (bs, 1H), 3.47 (m, 1H), 1.47 (m, 4H), 1.00 (t, J = 6.6, 3H).

<u>EXAMPLE 17</u>

<u>(±)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **117**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *n*-Pr, R^{13} = CH_3)</u>

Compound **117** was prepared according to General Method 5 (EXAMPLE 2) from (±)-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (18 mg, 0.05 mmol), 37% aqueous formaldehyde (0.01 mL, 0.3 mmol, 5 eq), sodium cyanoborohydride (16 mg, 0.3 mmol, 5 eq) in 1 mL acetic acid (0.05 M) stirred at rt for 12 h to afford 7 mg of (3*R/S*)-3,4-dihydro-8-isopropoxy-4-methyl-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (7 mg, 0.02 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of a 1:1 acetic acid:concentrated HCl (5 mM) and heated at 90°C for 6 h to afford 5 mg (83%) of Compound **117** after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 10.83 (bs, 1H), 7.11 (s, 1H), 6.99 (d, J = 8.8, 1H), 6.87 (d, J = 8.8, 1H), 4.28 (dd, J = 10.7, 2.2, 1H), 4.07 (dd, J = 10.7, 2.4, 1H), 3.24 (m, 1H), 2.97 (s, 3H) 1.48 (m, 4H), 0.96 (t, J = 7.3, 3H).

EXAMPLE 18

(±)-4-Ethyl-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **118**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *n*-Pr, R^{13} = CH_2CH_3)

Compound **118** was prepared according to General Method 6 (EXAMPLE 3) from (±)-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (11 mg, 0.03 mmol) and $NaBH_4$ pellets (>10 equiv) in 1 mL acetic acid (0.03 M) stirred at rt for 12 h to afford 9 mg of (±)-4-ethyl-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (9 mg, 0.02 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of 1:1 acetic acid:concentrated HCl (5.9 mM) and heated at 90°C for 6 h to afford 6 mg (75%) of Compound **118** after flash chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.91 (bs, 1H), 7.12 (s, 1H), 7.07 (d, J = 8.8, 1H), 6.96 (d, J = 8.8, 1H), 4.27 (dd, J = 10.3, 2.0, 1H), 3.90 (dd, J = 10.3, 2.7, 1H), 3.44 (m, 1H), 3.27 (m, 1H), 3.26 (m, 1H), 1.52 (m, 2H), 1.41 (m, 2H), 1.18 (t, J = 7.1, 3H) 0.94 (t, J = 7.3, 3H).

EXAMPLE 19

(±)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **119**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *n*-Pr, R^{13} = CH_2CF_3)

Compound **119** was prepared according to General Method 6 (EXAMPLE 3) from (±)-3,4-dihydro-8-isopropoxy-3-propyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (16 mg, 0.05 mmol) and $NaBH_4$ pellets (>10 equiv) in 11 mL trifluoroacetic acid (0.04 M) stirred at rt for 12 h to afford 27 mg of (±)-3,4-dihydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (27 mg, 0.06 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 1:1 acetic acid:concentrated HCl (0.03M) and heated at 90°C for 6 h to afford 11 mg (50% for the 2

steps) of Compound **119** after flash chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.78 (bs, 1H), 7.14 (s, 1H), 7.07 (d, *J* = 8.8, 1H), 6.95 (d, *J* = 8.8, 1H), 4.35 (dd, *J* = 10.7, 1.5, 1H), 3.99 (dd, *J* = 10.7, 2.4, 1H), 3.83 (m, 1H), 3.72 (m, 1H), 3.32 (m, 1H), 1.51 (m, 2H), 1.42 (m, 2H), 0.93 (t, *J* = 7.3, 3H).

EXAMPLE 20

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **120**, Structure 9 of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr)

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-3'-methyl-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure 7 of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr): This compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.755 g, 2.16 mmol), (*R*)-*N*-*t*-Boc valinol (0.701 g, 3.45 mmol), triphenylphosphine (0.905 g, 3.45 mmol), DIAD (0.679 mL, 3.45 mmol) and *N*-methylmorpholine (1.5 mL) in THF (20 mL) to afford 0.79 g (68%) of (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-3'-methyl-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline, a tan solid. R_f 0.4 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, 1H, *J* = 9.0), 7.55 (d, 1H, *J* = 9.0), 7.30 (s, 1H), 5.52 (septet, 1H, *J* = 6.2), 4.81-4.75 (m, 1H), 4.14-3.90 (m, 3H), 2.15-2.01 (m, 1H), 1.46 (s, 9H), 1.41 (d, 6H, *J* = 6.2), 0.99-0.96 (m, 6H).

(3*R*)-3,4-Dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline: This compound was prepared according to General Method 2 (EXAMPLE 1) from (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-3'-methyl-1'-pentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (0.79 g, 1.5 mmol) in CH_2Cl_2 (10 mL) and TFA (10 mL) to afford (2'*R*)-6-bromo-5-(2'-amino-3'-methyl-1'-pentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (0.52 g, 80% yield). This material (0.52 g, 1.2 mmol) was carried on according to General Method 3 (EXAMPLE 1) by treatment with $Pd_2(dba)_3$ (0.021 g,

2 mol%), (±)-BINAP (0.030 g, 4 mol%) and *t*-BuONa (0.158 g, 1.64 mmol) in toluene (7 mL) to afford 0.320 g (77%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid. R_f 0.4 (9:1 hexane:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, 1H, *J* = 8.7), 7.18 (s, 1H), 7.04 (d, 1H, *J* = 8.7), 5.47 (septet, 1H, *J* = 6.1), 4.36 (dd, *ABX*, 1H, *J* = 10.6, 2.8), 3.97 (dd, *ABX*, 1H, *J* = 10.6, 7.5), 3.87 (broad s, 1H), 3.29-3.21 (m, 1H), 1.83-1.74 (m, 1H), 1.38 (d, 6H, *J* = 6.2), 1.06 (d, 3H, *J* = 6.8), 1.03 (d, 3H, *J* = 6.8).

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **120**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr):

Compound **120** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.006 g, 0.017 mmol) in conc. HCl (0.5 mL) and AcOH (1.0 mL) to afford Compound **120** (0.005 g, 100% yield), a yellow solid. R_f 0.4 (9:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.48 (broad s, 1H), 7.12 (s, 1H), 6.93 (s, 2H), 4.37 (dd, *ABX*, 1H, *J* = 10.6, 2.8), 3.97 (dd, *ABX*, 1H, *J* = 10.4, 7.5), 3.81 (broad s, 1H), 3.26-3.16 (m, 1H), 1.83-1.71 (m, 1H), 1.06 (d, 3H, *J* = 6.7), 1.03 (d, 3H, *J* = 6.7).

EXAMPLE 21

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **121**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_3)

Compound **121** was prepared according to General Method 5 (EXAMPLE 2) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.010 g, 0.028 mmol) with paraformaldehyde (0.008 g, 0.280 mmol) and $NaCNBH_3$ (0.009 g, 0.140 mmol) in AcOH (1 mL) to afford 0.009 g (90%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-4-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. This material (0.009 g, 0.025 mmol) was carried on according to

General Method 4 (EXAMPLE 1) by treatment with conc. HCl (0.5 mL) and AcOH (1 mL) to afford 0.006 g (86%) of Compound **121** as a yellow solid. R_f 0.6 (9:1 CH_2Cl_2;MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.49 (broad s, 1H), 7.13 (s, 1H), 7.06 (d, 1H, J = 8.9), 7.02 (d, 1H, J = 8.9), 4.43 (dd, *ABX*, 1H, J = 10.9, 1.8), 3.86 (dd, *ABX*, 1H, J = 10.9, 2.9), 3.03 (s, 3H), 2.93-2.88 (m, 1H), 2.02-1.91 (m, 1H), 0.99 (d, 3H, J = 6.9), 0.95 (d, 3H, J = 6.9).

EXAMPLE 22

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **122**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*Pr, R^{13} = CH_2CH_3)

Compound **122** was prepared according to General Method 5 (EXAMPLE 2) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (50 mg, 0.14 mmol) and $NaBH_4$ pellets (>10 equiv) in 2 mL acetic acid to afford 30 mg (*ca.* 60%) of (3*R*)-4-ethyl-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (30 mg, 0.08 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of 1:1 acetic acid:concentrated HCl (0.02M) heated at 90°C for 4 h to afford 15 mg (57%) of Compound **122**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.87 (bs, 1H), 7.13 (d, J = 9.3, 1H), 7.12 (s, 1H), 6.96 (d, J = 8.9, 1H), 4.49 (d, J = 10.8, 1H), 3.69 (dd, J = 10.7, 2.7, 1H), 3.49 (m, 1H), 3.24 (m, 1H), 2.88 (bd, J = 7.9, 1H) 1.83 (m, 1H), 1.64 (t, J = 7.1, 3H), 0.98 (d, J = 10.6, 3H), 0.96 (d, J = 10.6, 3H).

EXAMPLE 23

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **123**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CF_3)

Compound **123** was prepared according to General Method 3 (EXAMPLE 1) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-

-*f*]quinoline (0.32 g, 0.90 mmol) with $NaBH_4$ (0.52 g, 14 mmol) in TFA (10 mL) to afford 0.39 g (100%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. This material (0.39 g, 0.90 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with conc. HCl (3 mL) in AcOH (6 mL) to afford 0.31 g (88%) of Compound **123**, a yellow solid. R_f 0.3 (19:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.87 (broad s, 1H), 7.20 (d, 1H, *J* = 8.9), 7.15 (s, 1H), 7.01 (d, 1H, *J* = 8.9), 4.58 (d, 1H, *J* = 10.8), 3.93-3.82 (m, 2H), 3.72-3.61 (m, 1H), 2.88 (d, 1H, *J* = 9.2), 1.81-1.74 (m, 1H), 1.00 (d, 3H, *J* = 6.2), 0.98 (d, 3H, *J* = 6.2).

EXAMPLE 24

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **124**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CClF_2)

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CClF_2): This compound was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)- 4-(2-chloro-2,2-difluoroethyl)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (30 mg, 0.1 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 3 mL chlorodifluoroacetic acid (0.03 M) stirred at rt for 12 h, to afford 22 mg (57%) of (3*R*)-4-ethyl-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.44 (d, J = 9.3, 1H), 7.30 (d, J = 9.3, 1H), 7.21 (s, 1H), 5.98 (m, 1H), 5.49 (m, 1H), 4.55 (dd, J = 10.7, 2.4, 1H), 3.84 (dd, J = 10.7, 2.4, 1H), 3.79 (m, 1H), 3.54 (m, 1H), 2.93 (m, 1H), 1.84 (m, 1H), 1.39 (d, J = 6.3, 3H), 1.38 (d, J = 6.3, 3H), 1.00 (d, J = 9.8, 3H), 0.99 (d, J = 9.8, 3H).

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **124**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CClF_2):

Compound **124** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-4-ethyl-3,4-dihydro-8-isopropoxy-3-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (22 mg, 0.02 mmol) in 2 mL acetic acid and 2 mL concentrated HCl and heated at 90°C for 4 h to afford 14 mg (72%) of Compound **124**, after purification by column chromatography (3:1 hexanes: EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 12.10 (bs, 1H), 7.25 (d, *J* = 9.3, 1H), 7.14 (s, 1H), 6.98 (d, *J* = 9.3, 1H), 4.58 (dd, *J* = 10.7, 1.3, 1H), 4.10 (m, 1H), 3.94 (dd, *J* = 10.7, 2.4, 1H), 3.78 (m, 1H), 2.96 (bd, *J* = 9.8, 1H), 1.81 (m, 1H), 1.00 (d, *J* = 6.8, 3H), 0.98 (d, *J* = 6.8, 3H).

EXAMPLE 25

(3*R*)-4-(2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **125**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CHF_2)

Compound **125** was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (30 mg, 0.1 mmol) and $NaBH_4$ pellets (large excess, >10 equiv) in 5 mL difluoroacetic acid (0.02 M) stirred at rt for 12 h, to afford 28 mg (79%) of (3*R*)-4-ethyl-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. ^{1}**H NMR** (500 MHz, $CDCl_3$) 7.44 (d, J = 9.3, 1H), 7.30 (d, J = 9.3, 1H), 7.21 (s, 1H), 5.98 (m, 1H), 5.49 (m, 1H), 4.55 (dd, J = 10.7, 2.4, 1H), 3.84 (dd, J = 10.7, 2.4, 1H), 3.79 (m, 1H), 3.54 (m, 1H), 2.93 (m, 1H), 1.84 (m, 1H), 1.39 (d, J = 6.3, 3H), 1.38 (d, J = 6.3, 3H), 1.00 (d, J = 9.8, 3H), 0.99 (d, J = 9.8, 3H). This material (13 mg, 0.03 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 3 mL acetic acid and 3 mL concentrated HCl heated at 90°C for 4 h to afford 8 mg (70 %) of Compound **125**, after purification by column chromatography (3:1 hexanes: EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.59 (bs, 1H), 7.15 (d, *J* = 8.8, 1H), 7.13 (s, 1H), 6.94 (d, *J* = 8.8, 1H), 5.96 (m, 1H), 4.55 (dd, *J* = 10.7, 1.3, 1H), 3.87 (dd, *J* = 10.7, 2.4, 1H),

3.74 (m, 1H), 3.50 (m, 1H), 2.91 (bd, $J = 8.8$, 1H), 1.80 (m, 1H), 1.00 (d, $J = 11.7$, 3H), 0.97 (d, $J = 11.7$, 3H).

EXAMPLE 26

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **126**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = *i*-Pr, R^{13} = CH_2CHCH_2)

A suspension of (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.010 g, 0.028 mmol) and K_2CO_3 (0.019 g, 0.140 mmol) in DMF (1.0 mL) was treated with allyl bromide (0.024 mL, 0.280 mmol) and heated at 50°C for 16 h. The reaction mixture was poured into 25 mL water and extracted with EtOAc (2 x 25 mL). The extracts were washed with 25 mL each water and brine, dried over $MgSO_4$, filtered and concentrated to a yellow oil. Column chromatography (5-10% EtOAc in hexane gradient) gave 0.010 g (91%) of (3*R*)-4-allyl-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil. This material (0.006 g, 0.015 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with conc. HCl (1.0 mL) heated at 70°C for 1 h to afford 0.004 g (80%) of Compound **126**, a yellow solid. R_f 0.6 (9:1 CH_2Cl_2;MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.82 (broad s, 1H), 7.12 (d, 1H, $J = 8.9$), 7.11 (s, 1H), 6.93 (d, 1H, $J = 8.9$), 5.92-5.81 (m, 1H), 5.27-5.17 (m, 2H), 4.48 (d, 1H, $J = 10.9$), 3.99 (dd, *ABX*, 1H, $J = 16.4, 5.8$),), 3.84 (dd, *ABX*, 1H, $J = 16.4, 5.8$), 3.77 (dd, *ABX*, 1H, $J = 10.9, 2.8$), 2.96-2.93 (m, 1H), 1.94-1.84 (m, 1H), 0.98 (d, 3H, $J = 6.7$), 0.96 (d, 3H, $J = 6.7$).

EXAMPLE 27

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **127**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph)

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-2'-phenylethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure 7 of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 =

trifluoromethyl, R^6 = Ph): This compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (500 mg, 1.43 mmol), (2*R*)-(–)-*N*-*t*-butoxycarbonyl-2-phenylglycinol (542 mg, 2.28 mmol), triphenylphosphine (615 mg, 2.28 mmol), diisopropyl azodicarboxylate (462 mg, 2.28 mmol) and 4-methylmorpholine (570 mg, 5.64 mmol) in 15 mL THF to afford 295 mg (36%) of (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-2'-phenylethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline, a colorless oil, after column chromatography (1:1 EtOAc:hexanes). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 9.0), 7.55 (d, 1H, *J* = 9.0), 7.39-7.24 (m, 6H), 5.52 (septet, 1H, *J* = 6.2), 5.23 (s, 1H), 4.11 (m, 2H), 4.02 (m, 1H), 1.45-1.20 (m, 15H).

(3*R*)-3,4-Dihydro-8-isopropoxy-3-phenyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph): This compound was prepared according to General Method 2 (EXAMPLE 1) from (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-2'-phenylethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (295 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) and TFA (5 mL) to give 243 mg (100%) of (2'*R*)-6-bromo-5-(2'-amino-2'-phenylethoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline, an amber oil. This material (243 mg, 0.52 mmol) was carried on according to General Method 3 (EXAMPLE 1), by treatment with $Pd_2(dba)_3$ (24 mg, 0.026 mmol), BINAP (32.2 mg, 0.052 mmol) and sodium *t*-butoxide (70 mg, 0.73 mmol) in 8 mL toluene to afford 123 mg (61%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-phenyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid, after column chromatography (9:1 hexanes:EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.63-7.02 (m, 8H), 5.49 (septet, 1H, *J* = 6.2), 4.62 (dd, 1H, *J* = 8.3, 3.2), 4.45 (dd, 1H, *J* = 10.6, 3.2), 4.12 (s, 1H), 4.02 (dd, 1H, *J* = 10.6, 8.3) 1.40 (d, 3H, *J* = 6.2), 1.39 (d, 3H, *J* = 6.2).

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **127**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph):

Compound **127** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-dihydro-8-isopropoxy-3-phenyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (33.3 mg, 0.086 mmol) in 4 mL AcOH and 4 mL conc. HCl to afford 15.5 mg (52%) of the Compound **127**, a yellow solid, after column chromatography (1:1 EtOAc:hexanes). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.6 (s, 1H), 7.40 (m, 5H), 7.14 (s, 1H), 7.00 (d, 1H, J = 8.6), 6.95 (d, 1H, J = 8.6), 4.58 (m, 1H), 4.44 (m, 1H), 4.03 (m, 2H).

EXAMPLE 28

(3*R*)- 2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **128**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph, R^{13} = CH_2CF_3)

(3*R*)-3,4-Dihydro-8-isopropoxy-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph, R^{13} = CH_2CF_3): This compound was prepared according to General Method 6 (EXAMPLE 3) from (3*R*)-3,4-dihydro-8-isopropoxy-3-phenyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (49.5 mg, 0.127 mmol) and $NaBH_4$ (300 mg, 7.9 mmol) in 5 mL TFA, to afford 50.7 mg (85%) of (3*R*)-3,4-dihydro-8-isopropoxy-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid, after column chromatography (1:3 CH_2Cl_2:hexanes). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.55-7.10 (m, 8H), 5.50 (septet, 1H, J = 6.2), 4,77 (dd, 1H, J = 4.4, 3.4), 4.39 (dd, 1H, J = 11.0, 3.4), 4.29 (dd, 1H, J = 11.0, 4.4), 4.10 (m, 1H), 3.66 (m, 1H), 1.40 (d, 6H, J = 6.2).

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **128**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph, R^{13} = CH_2CF_3):

Compound **128** was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-dihydro-8-isopropoxy-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (50.7 mg, 0.11 mmol) in 2 mL AcOH and 2 mL conc. HCl to

afford 32.4 mg (70%) of the Compound **128**, a yellow solid, after column chromatography (1:1 EtOAc:hexane). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.0 (s, 1H), 7.40-7.05 (m, 8H), 4.74 (dd, 1H, J = 4.6, 3.2), 4.39 (dd, 1H, J = 11.0, 3.2), 4.29 (dd, 1H, J = 11.0, 4.6), 4.04 (m, 1H), 3.63 (m, 1H).

EXAMPLE 29

(3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **129**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = Ph, R^{13} = CH_2-cyclopropyl)

Compound **129** was prepared according to General Method 5 (EXAMPLE 2) from Compound **128** (EXAMPLE 28) (11.6 mg, 0.034 mmol), cyclopropanecarboxaldehyde (282 mg, 4.0 mmol), AcOH (104 mg, 1.75 mmol) and $NaCNBH_3$ (150 mg, 2.39 mmol) in 3 mL MeOH to afford 8.4 mg (63%) of Compound **129**, a yellow solid, after column chromatography (1:1 EtOAc:hexane). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.2 (s, 1H), 7.40-7.25 (m, 6H), 7.14 (s, 1H), 7.07 (d, 1H, J = 9.0), 4.77 (dd, 1H, J = 6.6, 3.6), 4.33 (dd, 1H, J = 10.9, 3.6), 4.15 (dd, 1H, J = 10.9, 6.6), 3.62 (dd, 1H, J = 15.3, 4.6), 2.65 (dd, 1H, J = 15.3, 7.9), 0.94 (m, 1H), 0.51 (m, 1H), 0.40 (m, 1H), 0.13 (m, 1H), -0.06 (m, 1H).

EXAMPLE 30

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **130**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = benzyl, R^{13} = CH_2CF_3)

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-3'-phenyl-1'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = benzyl): This compound was prepared according to General Method 1 (EXAMPLE 1) from the bromophenol (525 mg, 1.5 mmol), (*R*)-(+)-*N*-*t*-butoxycarbonyl-2-amino-3-phenyl-1-propanol (603 mg, 2.4 mmol), triphenylphosphine (646 mg, 2.4 mmol), diisopropyl azodicarboxylate (514 mg, 2.5 mmol) and *N*-methylmorpholine (607 mg, 6.0 mmol) in 15 mL THF to afford 212 mg (24%) of (2'*R*)-6-bromo-5-[(2'-*t*-

butoxycarbonylamino)-3'-phenyl-1'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline, a colorless oil, after column chromatography (1:9 EtOAc:hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, 1H, *J* = 9.0), 7.54 (d, 1H, *J* = 9.0), 7.32-7.18 (m, 6H), 5.52 (septet, 1H, *J* = 6.2), 4.87 (s, 1H), 4.36 (m, 1H), 4.03 (m, 2H), 3.09 (m, 1H), 1.45-1.20 (m, 15H).

(3*R*)-3-Benzyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = benzyl): This compound was prepared according to General Method 2 (EXAMPLE 1) from (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-3'-phenyl-1'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (212 mg, 0.365 mmol) in CH_2Cl_2 (5 mL) and TFA (5 mL) to give 176 mg (100%) of (2'*R*)-6-bromo-5-(2'-amino-3'-phenyl-1'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline, an amber oil. This material (176 mg, 0.365 mmol) was carried on according to General Method 3 (EXAMPLE 1) by treatment with $Pd_2(dba)_3$ (16.7 mg. 0.018 mmol), BINAP (22.7 mg, 0.036 mmol) and sodium t-butoxide (52.6 mg, 0.55 mmol) in 10 mL toluene to afford 26.2 mg (18%) of (*R*)-3-benzyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid, after column chromatography (1:9 EtOAc:hexane). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42-7.15 (m, 7H), 6.96 (d, 1H, *J* = 9.0), 5.47 (septet, 1H, *J* = 6.2), 4.35 (dd, 1H, *J* = 2.8, 10.5), 4.02 (dd, 1H, *J* = 10.5, 6.6), 3.82 (s, 1H), 3.75 (m, 1H), 2.91 (dd, 1H, *J* = 5.6, 13.3), 2.75 (dd, 1H, *J* = 8.6, 13.3), 1.38 (d, 3H, *J* = 6.2), 1.37 (d, 3H, *J* = 6.2).

(3*R*)-3-Benzyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = benzyl, R^{13} = CH_2CF_3): This compound was prepared according to General Method **6** (EXAMPLE 3) from (3*R*)-3-benzyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (25.8 mg, 0.064 mmol) and $NaBH_4$ (300 mg, 7.9 mmol) in 3 mL TFA, to afford 29.6 mg (95%) of (3*R*)-3-benzyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid, after column chromatography (1:9 EtOAc:hexane). **^{1}H NMR** (400 MHz, $CDCl_3$)

δ 7.51-7.10 (m, 8H), 5.51 (septet, 1H, J = 6.2), 4.29 (d, 1H, J = 10.5), 3.91 (m, 2H), 3.70-3.50 (m, 2H), 2.90 (dd, 1H, J = 6.3, 13.3), 2.80 (dd, 1H, J = 9.2, 13.3), 1.39 (d, 6H, J = 6.2).

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **130**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = benzyl, R^{13} = CH_2CF_3):

Compound **130** was prepared according to General Method **4** (EXAMPLE 1) from (3*R*)-3-benzyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (29.6 mg, 0.061 mmol) in AcOH (3 mL) and conc. HCl (3 mL) to afford 20.2 mg (75%) of the Compound **130**, a yellow solid, after column chromatography (1:1 EtOAc:hexane). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.0 (s, 1H), 7.37-7.04 (m, 8H), 4.29 (d, 1H, J = 10.6), 3.93-3.80 (m, 2H), 3.65-3.48 (m, 2H), 2.90 (dd, 1H, J = 6.2, 13.3), 2.78 (dd, 1H, J = 9.2, 13.3).

EXAMPLE 31

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **131**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, R^6, R^7, R^8 = H, R^2 = trifluoromethyl)

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)ethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, R^6, = H, R^2 = trifluoromethyl): This compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (533 mg, 1.52 mmol), *N*-butoxycarbonyl ethanolamine (270 mg, 1.67 mmol), triphenylphosphine (438 mg, 1.67 mmol) and DIAD (0.33 mL, 1.67 mmol) in 15 mL THF to afford 317 mg (42%) of 6-bromo-5-[(2'-*t*-butoxycarbonylamino)ethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline after purification by flash chromatography (silica gel, 100% hexanes to 10% ethyl acetate/hexanes, gradient elution). ^{1}**H NMR** ($CDCl_3$) δ 7.80 (d, J = 9.0, 1H), 7.56 (d, J = 9.0, 1H), 7.30 (s, 1H), 5.53 (m, 1H), 5.19 (br s, 1H), 4.08 (m, 2H), 3.60 (m, 2H), 1.48 (s, 9H), 1.41 (d, J = 6.1, 6H).

3,4-Dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, R^6, = H, R^2 = trifluoromethyl): This compound was prepared according to General Method 2 (EXAMPLE 1) from 6-bromo-5-[(2'-*t*-butoxycarbonylamino)ethoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (208 mg, 0.42 mmol) in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid to afford 78 mg (47%) of 6-bromo-5-(2'-aminoethoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline. This material (78 mg) was carried on according to General Method 3 (EXAMPLE 1) by treatment with sodium tert-butoxide (26.9 mg, 0.28 mmol), BINAP (5.0 mg, 0.008 mmol), $Pd_2(dba)_3$ (3.7 mg, 0.004 mmol) and toluene (1.3 mL) heated at reflux overnight to afford 52.5 mg (84%) of 3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow oil, after flash chromatography (2% ethyl acetate/hexanes to 50% ethyl acetate/hexanes, gradient elution). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.8, 1H), 7.18 (s, 1H), 7.03 (d, J = 8.8, 1H), 5.47 (m, 1H), 4.67 (br s, 1H), 4.31 (dd, J = 4.5, 4.3, 2H), 3.54 (dd, J = 4.4. 4.3, 2H), 1.38 (d, J = 6.2, 6H).

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **131**, Structure 9 of **Scheme II**, where R^1, R^3, R^4, R^5, R^6, = H, R^2 = trifluoromethyl):

Compound **131** was prepared according to General Method 4 (EXAMPLE 1) from 3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (10 mg, 0.032 mmol) in 0.64 mL glacial acetic acid and 0.32 mL conc. HCl heated at 70°C for 90 minutes to afford 5 mg of Compound **131** after flash chromatography (4:1 hexanes:EtOAc). ^{1}**H NMR** (400 MHz, acetone-d_6) δ 10.85 (br s, 1H), 7.01 (d, J = 8.62, 1H), 6.91 (d, J = 8.64, 1H), 6.86 (s, 1H), 4.26 (m, 2H), 3.46 (m, 2H).

EXAMPLE 32

2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **132**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^{13} = CH_2CF_3)

Compound **132** was prepared according to General Method 3 (EXAMPLE 1) from 3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (20.0 mg, 0.064 mmol) and sodium borohydride (excess of 20 mg) in 3 mL trifluoroacetic acid to afford 25 mg (*ca.* 100%) of 3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a red oil. No further purification was performed and the material was directly transformed according to General Method 4 (EXAMPLE 1) from 3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (25 mg) in 0.32 mL conc. HCl and 0.64 mL glacial acetic acid heated at 70°C for 90 minutes to afford 11 mg (49%) of Compound **132** after purification by flash chromatography (9:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.05 (br s, 1H), 7.31 (d, J = 9.0, 1H), 7.04 (d, J = 8.8, 1H), 6.92 (s, 1H), 4.32 (t, J = 4.3, 2H), 4.14 (q, J = 9.5, 2H), 3.61 (t, J = 4.4, 2H).

EXAMPLE 33

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-7-methyl-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound 133, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$, R^{13} = CH_3)

(2'*R*)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-cyclopentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure 7 of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$): The compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.50 g, 1.43 mmol), (1*R*,2*R*)-2-*N*-t-butoxycarbonylamino-1-cyclopentanol (460 mg, 2.28 mmol), triphenylphosphine (600 mg, 2.28 mmol) and diisopropyl azodicarboxylate (0.45 ml, 2.28 mmol) in 0.6 mL *N*-methylmorpholine in 14 mL

dry THF to afford 190 mg (25%) of (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-cyclopentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline after flash chromatography (100% hexanes to 6:1 hexanes/EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.8, 1H), 7.49 (d, J = 8.8, 1H), 7.24 (s, 1H), 5.52 (m, 1H), 5.28 (d, J = 9.3, 1H), 4.96 (m, 1H), 4.11 (m, 1H), 2.04 (m, 2H), 1.82 (m, 2H), 1.59 (m, 2H), 1.45 (s, 9H), 1.42 (d, J = 7.8, 3H), 1.41 (d, J = 7.8, 3H).

<u>(2'*R*)-6-Bromo-5-(2'-amino-1'-cyclopentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline</u>: This compound was prepared according to General Method 2 (EXAMPLE 1) from (2'*R*)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-1'-cyclopentoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (190 mg, 0.35 mmol) in 3 mL CH_2Cl_2 and 3 mL TFA to afford 133 mg (86 %) of (2'*R*)-6-bromo-5-(2'-amino-1'-cyclopentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline.

<u>(7a*R*,10a*S*)-3-Isopropoxy-1-(trifluoromethyl)-7,7a,8,9,10,10a-hexahydrocyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$)</u>: This compound was prepared according to General Method 3 (EXAMPLE 1) from (2'*R*)-6-bromo-5-(2'-amino-1'-cyclopentoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (133 mg, 0.37 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (7.6 mg, 4 mol%), $Pd_2(dba)_3$ (5.6 mg, 2 mol%), sodium *t*-butoxide (41 mg, 1.19 mmol) to afford 73 mg (68%) of (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline after purification by flash chromatography (100% hexanes to 4:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.8, 1H), 7.18 (s, 1H), 7.04 (d, J = 8.8, 1H), 5.47 (m, 1H), 4.13 (m, 1H), 4.06 (s, 1H), 3.78 (m, 1H), 2.06 (m, 2H), 1.96 (m, 2H), 1.65 (m, 2H), 1.38 (d, J = 5.9, 3H), 1.37 (d, J = 6.4, 3H)

<u>(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-7-methyl-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **133**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$, R^{13} = CH_3)</u>:

Compound **133** was prepared according to General Method 5 (EXAMPLE 2) from (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline (5 mg, 0.014 mmol), 37% aqueous formaldehyde solution (0.01 mL, 0.14 mmol) and $NaBH_3CN$ (9 mg, 0.14 mmol) in 1 mL acetic acid to afford 5 mg of (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-7-methyl-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline. This material (5 mg, 0.01 mmol) carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of 1:1 acetic acid:concentrated HCl (3 mM) heated at 90°C for 4 h to afford 3.9 mg (90%) of Compound **133**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 10.58 (bs, 1H), 7.10 (s, 1H), 7.00 (d, J = 8.8, 1H), 6.87 (d, J = 8.8, 1H), 4.15 (m, 1H), 3.53 (m, 1H), 2.98 (s, 3H), 2.02 (m, 4H), 1.64 (m, 2H), 0.88 (t, J = 6.8, 3H).

EXAMPLE 34

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **134**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$, R^{13} = CH_2CH_3)

Compound **134** was prepared according to General Method 5 (EXAMPLE 2) from (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline (5 mg, 0.014 mmol) and $NaBH_4$ pellets (>10 equiv) in 5 mL acetic acid to afford 5 mg of (7a*R*,10a*S*)-7-ethyl-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline. This material (5 mg, 0.01 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of 1:1 acetic acid:concentrated HCl (3 mM) and heated at 90°C for 4 h to afford 4 mg (89%) of Compound **134**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.01 (bs, 1H), 7.10 (s, 1H), 7.01 (d, J = 8.8, 1H), 6.90 (d, J = 8.8, 1H), 4.00 (m, 1H), 3.59 (ddd, J = 10.0, 7.1, 3.4 1H), 3.44 (m, 2H), 2.03 (m, 4H), 1.61 (m, 2H), 1.20 (t, J = 7.1, 3H).

EXAMPLE 35

7,7a,8,9,10,10a-Hexahydro-7-(2,2,2-trifluoroethyl)1-(trifluoromethyl)--4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one (Compound **135**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$, R^{13} = CH_2CF_3)

Compound **135** was prepared according to General Method 6 (EXAMPLE 3) from (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline (20 mg, 0.057 mmol) and $NaBH_4$ pellets (excess) in 7 mL TFA to afford 20 mg of (7a*R*,10a*S*)-7,7a,8,9,10,10a-hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinoline. This material (20 mg, 0.046 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 6 mL of 1:1 acetic acid:concentrated HCl (0.01M) heated at 90°C for 4 h to afford 15 mg (83%) of Compound **135**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 12.10 (bs, 1H), 7.15 (s, 1H), 7.10 (d, *J* = 8.8, 1H), 7.01 (d, *J* = 8.8, 1H), 4.14 (m , 1H), 3.94 (m, 2H), 3.72 (ddd, *J* = 10.5, 7.6, 3.4, 1H), 2.18 (m, 2H), 2.01 (m, 2H), 1.68 (m, 2H).

EXAMPLE 36

(±)-(2'*S*,3'*R*,)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **136**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = Me, R^{13} = CH_2CF_3)

(±)-(2'*S*,3'*R*,)-6-Bromo-5-[(3'-*t*-butoxycarbonylamino)-2'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^3, R^6 = Me). The compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.30 g, 0.8 mmol), (±)-(2*R*,3*R*)-3-*N*-t-butoxycarbonyl-2-butanol (405 mg, 2.14 mmol), triphenylphosphine (562 mg, 2.14 mmol) and diisopropyl azodicarboxylate (0.42 ml, 2.14 mmol) in 0.24 mL *N*-methylmorpholine in 15 mL dry THF to afford 124 mg (28%) of (±)-(2'*S*,3'*R*,)-6-bromo-5-[(3'-*t*-butoxycarbonylamino)-2'-butoxy]-2-isopropoxy-4-

(trifluoromethyl)quinoline after flash chromatography (100% hexanes to 6:1 hexanes/EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.8, 1H), 7.49 (d, *J* = 8.8, 1H), 7.25 (s, 1H), 5.52 (m, 1H), 4.93 (m, 1H), 4.84 (m, 1H), 3.97 (m, 1H), 1.45 (s, 9H), 1.43 (d, *J* = 5.9, 3H), 1.40 (d, *J* = 6.4, 3H), 1.21 (d, *J* = 5.4, 3H), 0.87 (d, *J* = 6.4, 3H).

<u>(±)-(2'*S*,3'*R*,)-6-Bromo-5-(3'-amino-2'-butoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline</u>. This compound was prepared according to General Method 2 (EXAMPLE 1) from (±)-(2'*S*,3'*R*,)-6-bromo-5-[(3'-*t*-butoxycarbonylamino)-2'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (124 mg, 0.24 mmol) in 4 mL CH_2Cl_2 and 4 mL TFA to afford 82 mg (82%) of (±)-(2'*S*,3'*R*,)-6-bromo-5-(3'-amino-2'-butoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline.

<u>(±)-(2*S*,3*R*)-3,4-Dihydro-8-isopropoxy-2,3-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = Me)</u>: This compound was prepared according to General Method 3 (EXAMPLE 1) from (±)-(2'*S*,3'*R*,)-6-bromo-5-(3'-amino-2'-butoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (82 mg, 0.19 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5 mg, 4 mol%), $Pd_2(dba)_3$ (3.5 mg, 2 mol%), sodium *t*-butoxide (26 mg, 0.27 mmol) to afford 31 mg (47%) of (±)- (2*S*,3*R*)-3,4-dihydro-8-isopropoxy-2,3-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, after purification by flash chromatography (100% hexanes to 4:1 hexanes:EtOAc, gradient elution). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8, 1H), 7.18 (s, 1H), 7.02 (d, *J* = 8.8, 1H), 5.47 (m, 1H), 4.36 (m, 1H), 3.79 (bs, 1H), 3.57 (m, 1H), 1.38 (d, *J* = 6.3, 3H), 1.37 (d, *J* = 6.3, 3H), 1.30 (d, *J* = 6.8, 3H), 1.19 (d, *J* = 6.3, 3H).

<u>(±)-(2*S*,3*R*)-3,4-Dihydro-8-isopropoxy-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = Me, R^{13} = CH_2CF_3)</u>: This compound was prepared according to General Method 6 (EXAMPLE 3) from (±)-(2*S*,3*R*)-3,4-dihydro-8-isopropoxy-2,3-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (17 mg, 0.05 mmol) and $NaBH_4$ pellets (>10 equiv) in 4 mL trifluoroacetic acid (0.01 M) to afford 12 mg (*ca.* 60%) of

(±)-(2*S*,3*R*)-3,4-dihydro-8-isopropoxy-2,3-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, which was carried on without purification.

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **136**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = Me, R^{13} = CH_2CF_3): Compound **136** was prepared by General Method 4 (EXAMPLE 1) from (±)-(2*S*,3*R*)-3,4-dihydro-8-isopropoxy-2,3-dimethyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (12 mg, 0.03 mmol) in 4 mL of a 1:1 acetic acid:concentrated HCl (0.01M) heated at 90°C for 4 h to afford 8 mg (75 %) of Compound **136**, a yellow solid, after column chromatography (3:1 hexanes:EtOAc to 1:1 hexanes:EtOAc, gradient elution). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.96 (bs, 1H), 7.14 (s, 1H), 7.08 (d, *J* = 9.3, 1H), 6.97 (d, *J* = 9.3, 1H), 4.20 (m, 1H), 3.77 (m, 2H), 3.34 (m, 1H), 1.41 (d, *J* = 6.3, 3H), 1.09 (d, *J* = 6.8, 3H).

EXAMPLE 37

(6a*R*)-6a,7,8,9-Tetrahydro-4-(trifluoromethyl)-1*H*, 6*H*-pyrrolo[1',2':4,5][1,4]oxazino-[2,3-*f*]quinolin-2-one (Compound **137**, Structure **17** of **Scheme III**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6, R^{13} = $-CH_2CH_2CH_2-$)

(*R*)-[1-(2-Fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol (Structure **14** of **Scheme III**, where R^3, R^4, R^5, R^7, R^8 = H, R^6, R^{13} = $-CH_2CH_2CH_2-$): A suspension of 3,4-difluoronitrobenzene (1.57 g, 9.8 mmol), (*R*)-2-pyrrolidinemethanol (1.0 g, 9.8 mmol) and K_2CO_3 (1.36 g, 9.8 mmol) in 30 mL DMF was heated at 75°C for 20 h, whereupon the mixture was partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (19:1 CH_2Cl_2:MeOH) afforded 2.27 g (96%) of (*R*)-[1-(2-fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol, an orange solid. R_f 0.17 (7:3 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, 1H, *J* = 9.1, 2.6), 7.89 (dd, 1H, *J* = 14.4, 2.6), 6.68 (t, 1H, *J* = 9.0), 4.25-4.32 (m, 1H), 3.60-3.75 (m, 3H), 3.40-3.50 (m, 1H), 1.95-2.15 (m, 4H), 1.43 (t, 1H, *J* = 5.8).

<u>(3a*R*)-2,3,3a,4-Tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (Structure **15** of **Scheme III**, where R^3, R^4, R^5, R^7, R^8 = H, R^6, R^{13} = $-CH_2CH_2CH_2-$):</u> A suspension of (*R*)-[1-(2-fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol (2.27 g, 9.4 mmol) and NaH (60% mineral oil suspension, 0.737 g, 18.9 mmol) in 35 mL THF was heated at reflux for 1 h. The reaction was quenched with phosphate buffer and the aqueous layer was extracted with EtOAc. The solution was filtered through Celite and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (3:2 EtOAc:hexanes) afforded 476 mg (22%) of (3a*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine, an orange solid. R_f 0.55 (3:2 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H, *J* = 9.2, 2.4), 7.74 (d, 1H, *J* = 2.4), 6.44 (d, 1H, *J* = 8.8), 4.56 (dd, 1H, *J* = 10.3, 3.4), 3.65-3.72 (m, 1H), 3.60 (broad t, 1H, *J* = 8.6), 3.44 (t, 1H, *J* = 10.0), 3.36 (td, 1H, *J* = 9.8, 7.3), 2.15-2.25 (m, 2H), 2.05-2.15 (m, 1H), 1.45-1.55 (m, 1H).

<u>(3a*R*)-7-Amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (Structure **16** of **Scheme III**, where R^3, R^4, R^5, R^7, R^8 = H, R^6, R^{13} = $-CH_2CH_2CH_2-$):</u> A suspension of (3a*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (0.470 g, 2.10 mmol) and 10% Pd-C (28 mg) in 15 mL EtOAc and 15 mL EtOH was stirred under a hydrogen atmosphere overnight. The mixture was filtered through Celite and concentrated to afford 0.39 g (98%) of (3a*R*)-7-amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine. R_f 0.55 (3:2 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.50 (d, 1H, *J* = 8.3), 6.32 (d, 1H, *J* = 2.4), 6.29 (dd, 1H, *J* = 8.3, 2.4), 4.31 (dd, 1H, *J* = 8.3, 1.5), 3.37-3.50 (m, 3H), 3.31 (broad s, 2H), 3.13 (broad q, 1H, *J* = 8.3), 2.07-2.15 (m, 1H), 1.90-2.05 (m, 2H), 1.40-1.50 (m, 1H).

<u>(6a*R*)-6a,7,8,9-Tetrahydro-4-(trifluoromethyl)-1*H*, 6*H*-pyrrolo[1',2':4,5][1,4]-oxazino-[2,3-*f*]quinolin-2-one (Compound **137**, Structure **17** of **Scheme III**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6, R^{13} = $-CH_2CH_2CH_2-$):</u> A solution of (3a*R*)-7-amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (0.390 g, 2.05 mmol) and ethyl 4,4,4-trifluoroacetoacetate (0.378 g, 2.05 mmol) in 14 mL benzene was heated at reflux for 16 h, whereupon the solvent was removed *in vacuo*. The resultant solid was treated with 7 mL concentrated sulfuric acid and heated to 100°C for several hours. The solution was poured

into ice and neutralized with 6N NaOH and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (92:8 CH_2Cl_2:MeOH) afforded 120 mg of an impure yellow solid. Further purification was performed by reverse phase HPLC (ODS, 5 micron, 10 x 250 mm, 3 mL/min) to afford 5 mg (*ca.* 1%) of Compound **137**. ^{1}**H NMR** (500 MHz, acetone-d_6) δ 10.8 (v. broad s, 1H), 7.07 (d, *AB*, 1H, *J* = 8.6), 7.04 (d, *AB*, 1H, *J* = 8.6), 6.88 (s, 1H), 4.59 (dd, 1H, *J* = 10.0, 3.8), 3.38-3.45 (m, 2H), 3.34 (t, 1H, *J* = 10.0), 3.16-3.22 (m, 1H), 2.12-2.22 (m, 2H), 2.00-2.10 (m, 2H), 1.50-1.60 (m, 2H).

EXAMPLE 38

2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **138**, Structure **17** of **Scheme III**, where R^1, R^5, R^6, R^7, R^8 = H, R^2 = trifluoromethyl, R^3, R^4, R^{13} = Me)

To a solution of 7-amino-3,4-dihydro-2,2,4-trimethyl-2*H*-1,4-benzoxazine (0.16 g, 0.83 mmol) in 6 mL toluene was added ethyl 4,4,4-trifluoroacetoacetate (0.18 mL, 1.25 mmol), then the mixture was heated at reflux for 3 h. The solvent was removed under reduced pressure to an oil. This oil was dissolved in 4 mL conc. H_2SO_4 and heated at reflux for 2 h and neutralized by pouring into cold NaOH solution. Flash chromatography afforded Compound **138**, a by-product of the reaction. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 10.81 (bs, 1H), 7.12 (s, 1H), 7.06 (d, *J* = 7.5, 1H), 7.01 (d, *J* = 7.5, 1H), 3.02 (s, 2H), 2.98 (s, 3H) and 1.36 (s, 6H).

EXAMPLE 39

(3*R*)-8-Chloro-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Compound **139**, Structure **19** of **Scheme IV**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CF_3)

A solution of Compound **110** (EXAMPLE 10) (48 mg, 0.13 mmol) in 1.3 mL phosphorus oxychloride was heated at 80°C for 4 h. The mixture was poured into cold water

(20 mL) and saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes:EtOAc 4:1) afforded 28 mg (56%) of Compound **139**, a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (d, J = 9.2, 1H), 7.67 (s, 1H), 7.42 (d, J = 9.2, 1H), 4.45 (d, J = 10.8, 1H), 4.00-4.15 (m, 1H), 3.99 (dd, J = 10.8, 2.2, 1H), 3.77-3.90 (m, 1H), 3.35-3.45 (m, 1H), 1.45-1.65 (m, 2H), 1.01 (t, J = 7.4, 3H).

EXAMPLE 40

(3*R*) -3-Ethyl-3,4-dihydro-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Compound **140**, Structure **20** of **Scheme IV**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CF_3, R^{18} = OMe)

A solution of Compound **139** (EXAMPLE 139) (10 mg, 0.025 mmol) and NaOMe (16 mg, 0.30 mmol) in 2 mL MeOH was heated at reflux for 18 h. The mixture was partitioned between saturated NH_4Cl (10 mL) and EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes:EtOAc 4:1) afforded 6 mg (60%) of Compound **140**, an off-white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.49 (d, J = 9.1, 1H), 7.29 (d, J = 9.1, 1H), 7.26 (s, 1H), 4.49 (dd, J = 10.7, 1.5, 1H), 4.04 (s, 3H), 3.97 (dd, J = 10.7, 2.4, 1H), 3.85-3.95 (m, 1H), 3.75-3.85 (m, 1H), 3.22-3.32 (m, 1H), 1.55-1.65 (m, 2H), 0.99 (t, J = 7.4, 3H).

EXAMPLE 41

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8-*H*-[1,4]oxazino[2,3-*f*]quinoline-8-one (Compound **110**, Structure **29** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CF_3)

(2*R*)-(+)-2-(2-Fluoro-4-nitrophenyl)amino-1-butanol (Structure **21** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et): A mixture of 118 g (0.74 mole) of 3,4-difluoronitrobenzene and 85 g (0.95 mole) of *R* -(+)-2-amino-1-butanol was dissolved in 400 mL of absolute ethanol. To this solution was then added 62.2 g (0.74 mole) of sodium bicarbonate. The suspension was stirred and heated at reflux temperature for 12 h when TLC

indicated complete conversion of the 3,4-difluoronitrobenzene. After cooling to room temperature, the reaction mixture was filtered with the aid of additional ethanol and the ethanol was then evaporated. The crude product thus obtained was distilled under reduced pressure (110-112°C, 2 mm Hg) to afford (2*R*)-(+)-2-(2-fluoro-4-nitrophenyl)amino-1-butanol as a red solid. Yield, 162g (96%). $[\alpha]_D$=+95.4 ($CHCl_3$, *c* 22.7); **^{1}H NMR** ($CDCl_3$) δ 7.88 (1H, dd, J = 2.4, 8.9), 7.76 (1H dd J = 2.4, 11.7), 6.66 (1H, dd, J = 8.7), 4.88 (1H, m), 3.76 (1H dd, J = 4.2, 11.2), 3.68 (1H, dd J = 4.2, 11.2), 3.52 (1H, m), 2.63 (1H, bs), 1.70 (1H, m), 1.59 (1H, m), 0.97 (3H, t, J = 7.5). **^{13}C NMR**: ppm 150.1, 147.7, 142.8, 142.7, 136.1, 122.3, 110.9, 110.7, 109.5, 63.6, 55.8, 24.4, 10.4.

<u>(2*S*,4*R*)-(–)-3-(2-Fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **22** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^A = trifluoromethyl) and (2*R*,4*R*)-(+)-3-(2-Fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **22** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^A = trifluoromethyl):</u> A 2-L three-necked RB flask equipped with a Dean-Stark condenser was charged sequentially with 172 g (0.75 mole) of (2*R*)-(+)-2-(2-fluoro-4-nitrophenyl)amino-1-butanol, 750 mL of toluene, 543 g (3.77 mole) of trifluoroacetaldehyde ethyl hemiacetal and 34.4 g of *p*-toluenesulfonic acid. The reaction mixture was refluxed with azeotropic removal of water for 10-12 h. After cooling to room temperature the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate, brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure to afford a mixture of the desired oxazolidines (2*S*,4*R*)-(–)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (*cis*-isomer) and (2*R*,4*R*)-(+)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (*trans*-isomer) as a low melting solid. The product was found to be a mixture of two diastereoisomers (cis/trans, 4:3). Total yield 230 g (100%). (2*S*,4*R*)-(–)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (*cis*-isomer): **^{1}H NMR** ($CDCl_3$) δ 8.01 (1H, dd, J = 2.5, 8.9), 7.95 (1H, dd J = 2.5, 13.1), 6.95 (1H, t, J = 8.7), 5.82 (1H, q, J = 4.6), 4.42 (1H, bt, J = 7.46), 4.27 (1H, m), 4.08 (1H, d, J = 8.5), 1.65 (1H, m), 1.49 (1H, m), 0.87 (3H, t, J = 7.4). ^{13}C-NMR: ppm 153.2,

150.7, 140.9, 136.8, 128.0, 125.1, 122.2, 121.2, 119.3, 118.5, 113.5, 113.2, 85.4, 71.4, 59.2, 26.1, 9.3.

<u>(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol (Structure **23** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^{13} = CH_2CF_3)</u>: A 2-L three-necked RB flask equipped with an addition funnel and mechanical stirrer was charged sequentially with 230 g (0.75 mole) of the mixture of (–)-(2*S*,4*R*)- and (+)-(2*R*,4*R*)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine, 1.0 Liter of dry chloroform and 290 g (2.5 mole) of triethylsilane. The solution stirred under an atmosphere of nitrogen and cooled to –78°C. 161 g (0.85 mole) of $TiCl_4$ was added in drops through the addition funnel. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for another 24 h. The reaction mixture was quenched with ice and then neutralized with aq. Na_2CO_3. The organic layers were washed with water, brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate: hexanes 1: 9) to afford (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol as a glassy solid. Yield 190 g (82%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.8, 2.4, 1H), 7.94 (dd, J = 13.2, 2.9, 1H), 7.37 (dd, J = 8.8, 8.8, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 3.57 (m, 1H), 1.78 (dd, J = 6.8, 4.4, 1H), 1.58 (dq, J = 7.8, 2.9, 2H), 0.95 (t, J = 7.3, 1H).

<u>(+)-(3*R*)-3-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **24** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^{13} = CH_2CF_3)</u>: A solution of 190 g (0.612 mole) of the crude (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol in 1 Liter of dry THF was added dropwise to a stirred suspension of 36.77 g (0.919 mole, 1.5 eq) of sodium hydride in 1.5 L of dry THF under nitrogen atmosphere. After complete addition, the reaction mixture was refluxed for 3 h when TLC of the reaction mixture indicated complete conversion. After cooling to room temperature, 400 mL of methanol was added to destroy excess sodium hydride. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate. The organic portions were combined, washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under

reduced pressure. The crude product thus obtained was purified by silica gel column chromatography (ethyl acetate: hexanes 1:9) to obtain (+)-(3*R*)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine as a yellow crystalline solid. Yield 71 g (40%). $[\alpha]_D$= + 56.6 ($CHCl_3$, *c* 7.8); ^{1}**H NMR** ($CDCl_3$) δ 7.80 (1H, dd, J = 2.56, 8.98), 7.71 (1H, d, J = 2.57), 6.72 (1H, d, J = 9.07), 4.34 (1H, dd, J = 1.44, 11.02), 4.12 (1H, m), 4.06 (1H, dd, J = 2.12, 11.04), 3.79(1H, m), 3.37 (1H, m), 1.68 (2H, m), 1.00 (3H, t, J = 7.54). ^{13}**C NMR**: ppm 142.6, 139.1, 138.6, 126.1, 118.6, 112.6, 110.8, 64.9, 58.9, 50.6, 22.5 and 10.3.

(3*R*)-3-Ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (Structure **26** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^{13} = CH_2CF_3, R^b = *t*-butyl): A solution of 35 g (0.121 mole) 7-nitrobenzoxazine in 700 mL of ethyl acetate containing 3.5 g of 10% palladium on carbon was hydrogenated under ambient pressure. The reaction mixture was stirred for 12 h at room temperature. When TLC of the reaction mixture indicated complete conversion, 14.2 g (0.18 mol) of pyridine was added to the solution. After stirring for an hour, 17.4 g of trimethylacetyl chloride was added dropwise to the reaction mixture and it was stirred for another 2 hours until TLC indicated the complete conversion. The reaction mixture was quenched with ice and the organic layers were washed with sodium bicarbonate solution, 0.5 N HCl and brine. The crude product thus obtained was subject to silica gel column chromatography (ethyl acetate: hexanes 1:9) to afford the desired (3*R*)-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine as a white solid. Yield 35 g (84%). $[\alpha]_D$= −24.0 ($CHCl_3$, *c* 1.5); ^{1}**H NMR** ($CDCl_3$) δ 7.12 (1H, b), 7.04 (1H, d, J = 2.45), 6.97 (1H, dd, J = 2.46, 6.2), 6.69 (1H, d, J = 8.66), 4.20 (1H, dd, J = 1.78, 10.77), 3.96 (1H, dd, J = 2.22, 10.68), 3.81 (1H, m), 3.68 (1H, m), 3.14 (1H, m), 1.57(2H, m), 1.29 (6H, s), 0.95(3H, t, J = 7.48). ^{13}**C NMR**: ppm 176.5, 144.3, 130.4, 129.7, 115.0, 114.3, 109.8, 65.0, 59.1, 53.8, 39.6, 27.9, 22.7,10.7.

(3*R*)-(−)-3-Ethyl-3,4-dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (Structure **27** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^{13} = CH_2CF_3, R^b = *t*-butyl): A solution of 35 g (0.102 mol) of (3*R*)-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine was

dissolved in 800 mL of dry ether under nitrogen atmosphere. The solution was then cooled to -30°C and 150 mL (1.7M in pentane, 0.255 mol) of *n*-BuLi was added dropwise. The reaction mixture was stirred at -30°C for one hour before it was allowed to warm to -8°C. The temperature of the reaction mixture was then maintained at -8°C to -5°C for 5 hours after which it was cooled down to -30°C. 57.9 g of ethyl trifluoroacetate (0.408 mol) was then added to the reaction mixture and the solution was allowed to warm up to room temperature overnight. The reaction mixture was poured in to aqueous ammonium chloride and extracted with ether. The organic portions were combined, washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography (ethyl acetate: hexanes 1: 9) to provide 25 g (56%) of (3*R*)-(–)-3-ethyl-3,4-dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine.

(3*R*)-8-[2-(1-Carbethoxyprop-1-enyl)]-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4–benzoxazine (Structure 28 of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = Et, R^{13} = CH_2CF_3, R^b = *t*-butyl): A 1-L round bottom flask was charged with 25 g (57 mmol) of (3*R*)-(–)-3-ethyl-3,4-dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine, 23.8 g (68.4 mmol) of (carbethoxymethylene)-triphenyl phosphorane and 500 mL of toluene. The solution was heated to reflux for 4-5 hours until TLC indicated that the starting material was gone. The toluene was evaporated and 500 mL of ether/hexane (1:1) was added to the crude product. The solution was then cooled down to -5°C for several hours and filtered. The filtrate was concentrated under reduced pressure and subject to silica gel column (ethyl acetate : hexane, 1: 4) to afford 28.5 g (93%) (3*R*)-8-[2-(1-carbethoxyprop-1-enyl)]-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4–benzoxazine as a brown oil. $[\alpha]_D$= –24.4 ($CHCl_3$, *c* 20.1); **^{1}H NMR** ($CDCl_3$) δ 8.83 (1H, b), 7.67 (1H, d, J = 9.01), 6.94 (1H, d, J = 8.99), 4.30 (1H, dd, J = 1.64, 10.80), 4.05 (1H, dd, J = 2.38, 10.82), 3.92 (1H, m), 3.69 (1H, m), 3.24 (1H, m), 1.59 (2H, m), 1.27 (6H, s), 0.96 (3H, t, J = 7.38). **^{13}C NMR**: ppm 186.4, 177.4, 144.3, 129.9,

129.4, 129.3, 126.6, 123.8, 121.0, 120.3, 119.7, 117.4, 116.4, 114.6, 113.5, 111.7, 65.6, 58.6, 52.7, 39.9, 27.7, 22.8, 10.4.

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8-*H*-[1,4]oxazino[2,3-*f*]quinoline-8-one (Compound **110**, Structure **29** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = Et, R^{13} = CH_2CF_3): 36 g (70.6 mmol) of (3*R*)-8-[2-(1-carbethoxyprop-1-enyl)]-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-7-(trimethylacetamido)-2*H*-1,4–benzoxazine was dissolved in 761 mL of acetic acid and 507 mL of concentrated hydrochloric acid. The solution was heated to reflux for 12 hours until TLC indicated the complete conversion of the starting material. The reaction mixture was then allowed to cool to room temperature. The reaction was neutralized with cold aqueous NaOH solution to pH 6-7 and extracted with EtOAc. The combined organic solution was evaporated and purified by silica gel column. (Ethyl acetate: hexane 1:1) chromatography and subsequent recrystallization from methanol to obtain 23 g of Compound **110** as a yellow solid. Yield: 86%. $[\alpha]_D = -42.0$ (EtOH, *c* 63.5); **^{1}H NMR** ($CDCl_3$) δ 12.9 (1H, b), 7.15 (1H, s), 7.13 (1H, d, J = 8.9), 7.05 (1H, d, J = 8.96), 4.37 (1H, d, J = 10.76), 3.97 (1H, dd, J = 2.04, 10.7), 3.84 (1H, m), 3.74 (1H, m), 3.23 (1H, m), 1.58 (2H, m), 0.97 (3H, t, J = 7.52). **^{13}C NMR**: ppm 162.2, 139.5, 137.8, 133.9, 127.8, 125.2, 123.7, 121.9, 121.0, 109.7, 106.5, 64.2, 58.4, 55.1, 22.9, 10.3.

EXAMPLE 42

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **141**, Structure **29** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2, R^6 = trifluoromethyl, R^{13} = $-CH_2CF_3$)

2-(2,2,2-Trifluoroethyl)amino-5-nitrophenol (Structure **30** of **Scheme VI**, where R^7, R^8 = H, R^{13} = CH_2CF_3): To a solution of 2-amino-5-nitrophenol (250 mg, 1.62 mmol) in 3 mL of trifluoroacetic acid stirred at 0°C, was added sodium borohydride (pellets, 375 mg, 9.91 mmol). The orange solution was allowed to slowly warm to rt and stirred for 12 h. The solution was diluted with 50 mL of water and cooled to 0°C. Solid potassium carbonate was

then slowly added until the pH reached 7. The solution was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with brine (25 mL), dried with anhydrous magnesium sulfate, filtered and concentrated to give an orange solid. Flash chromatography (7:3 hexanes:EtOAc) afforded 0.32 g (83%) of 2-(2,2,2-trifluoroethyl)amino-5-nitrophenol, a yellow solid. ^{1}**H NMR** (400 MHz, acetone-d_6) 9.48 (broad s, 1H), 7.79 (dd, 1H, *J* = 9.1, 2.4), 7.67 (d, 1H, *J* = 2.4), 6.96 (d, 1H, *J* = 8.8), 6.20 (broad s, 1H), 4.26-4.18 (m, 2H).

(±)-3,4-Dihydro-3-hydroxy-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (Structure **24** of **Scheme VI**, where R^3, R^4, R^7, R^8 = H, R^5 = OH, R^6 = trifluoromethyl, R^{13} = CH_2CF_3): To solution of 2-(trifluoroethyl)amino-5-nitrophenol (100 mg, 0.45 mmol) and potassium carbonate (250 mg, 1.81 mmol) in 0.5 mL of dry dimethyformamide pre-heated to 65-75°C was added 1-bromo-3,3,3-trifluoroacetone (0.28 mL, 2.70 mmol) *via* a syringe pump over 2 h. The crimson solution was then allowed to stir for 2-3 hours at 65-75°C, then the solution was allowed to cool to room temperature, extracted with ethyl acetate (2 x 50 mL) and washed with brine (25 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to give a brown oil. The crude oil was purified *via* flash chromatography (4:1 hexanes:EtOAc) to afford 97 mg (63%) of (±)-3,4-dihydro-3-hydroxy-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine. ^{1}**H NMR** (400 MHz, $CDCl_3$) d 7.89 (dd, 1H, *J* = 7.8,2.5), 7.80 (d, 1H, *J* = 2.5), 6.94 (d, 1H, *J* = 9.1), 4.71 (d, 1H, *J* = 11.5), 4.51-4.63 (s, 1H), 4.08-4.12 (m, 1H), 4.00-4.06 (m, 2H).

(±)-3,4-Dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (Structure **24** of **Scheme VI**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = trifluoromethyl, R^{13} = CH_2CF_3): To a solution of (±)-3,4-dihydro-3-hydroxy-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (0.10 g, 0.29 mmol) in 3 mL of trifluoroacetic acid and then sodium cyanoborohydride (3.0 g, 47.4 mmol) was slowly added *via* an solid addition funnel under nitrogen at 0°C over the course of 30 minutes the reaction was allowed to warm to rt and stirred for 12 hours. The reaction mixture was then diluted with water and cooled to

0°C. Solid potassium carbonate was then added slowly to pH 7. The solution was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered and evaporated under reduced pressure to give an oil. The oil was purified *via* flash chromatography (7:3 hexanes:EtOAc) to afford 51 mg (52%) of (±)-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine. ^{1}**H NMR** (400 MHz, $CDCl_3$) d 7.87 (dd, 1H, J = 9.1, 2.8), 7.81 (d, 1H, J = 2.5), 6.92 (d, 1H, J = 9.1), 4.73 (d, 1H, J = 12.1), 4.48-4.39 (m, 1H), 4.13-4.06 (m, 2H), 3.99-3.88 (m, 1H).

<u>(±)-7-Amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (Structure 25 of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = trifluoromethyl, R^{13} = CH_2CF_3)</u>: To a solution of (±)-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (100 mg, 0.30 mmol) in 1.5 mL ethyl acetate was added 10% Pd-C (42 mg). The reaction mixture was then purged with nitrogen and then purged with hydrogen. A hydrogen balloon was then inserted through a septum into the reaction mixture and allowed to stir for 3 hours at room temperature. The solution was then filtered through a pad of celite and rinsed with ethyl acetate. The solvent was evaporated under reduced pressure to give a crude brown oil which was purified *via* flash chromatography (2:1 hexanes:EtOAc) to afford 85 mg (93%) (±)-7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine. ^{1}**H NMR** (400 MHz, $CDCl_3$) 6.68 (d, 1H, J = 8.4), 6.32-6.28 (m, 2H), 4.56 (dd, 1H, J = 12.0, 0.96), 4.16-4.00 (m, 2H), 3.84-3.69 (m, 2H), 3.60-3.32 (m, 2H).

<u>(±)-3,4-Dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (Structure 26 of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = trifluoromethyl, R^{13} = CH_2CF_3, R^b = *t*-butyl)</u>: To a solution of (±)-7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (140 mg, 0.47 mmol) in 5 mL EtOAc was added trimethylacetyl chloride (0.085 mL, 0.70 mmol) and anhydrous pyridine (0.056 mL, 0.70 mmol). The solution was allowed to stir at rt for 12 h. The solution was then washed sequentially with saturated sodium bisulfate (2 x 10 mL), copper sulfate (10 mL) and

brine (10 mL). The organic phase was dried with anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure to yield an oil. The oil was purified *via* flash chromatography (7:3 hexanes:EtOAc) to afford 160 mg (89%) of (±)-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylpropionamido)-2*H*-1,4-benzoxazine. **^{1}H NMR** ($CDCl_3$, 400 MHz) d 1.25 (s, 9H), 3.78 (sext, J = 8.0 Hz, 1H), 3.88 (m, 1H), 4.02 (m, 1H), 4.22 (sext. J = 8.3 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 6.77 (d, J = 8.8 Hz, 1H), 7.05 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 7.11 (d, J = 2.44 Hz, 1H), 7.15 (s, 1H).

<u>(±)-3,4-Dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (Structure **27** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^2, R^6 = trifluoromethyl, R^{13} = CH_2CF_3, R^b = *t*-butyl)</u>: To a solution of (±)-7-(2,2-dimethylpropionamido)-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (200 mg, 0.52 mmol) in 3 mL of dry diethyl ether at –30°C was added *t*-butyllithium (1.7M/ pentane, 0.80 mL, 1.35 mmol) was added dropwise over of 30 min and then stirred at –10°C. The deep yellow solution was allowed to stir at –10°C for 5-6 hours and then recooled to –30°C and trifluoroethyl acetate (0.186 mL, 1.56 mmol) was slowly added. The reaction was allowed to gradually warm to room temperature over the course of 12 hours. The reaction was quenched with saturated ammonium chloride (2 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give a brown oil. The substrate was purified *via* flash chromatography (4:1 hexanes:EtOAc) to afford 40 mg (15 %) of (±)-3,4-dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine. **^{1}H NMR** (400 MHz, $CDCl_3$) d 8.92 (s, 1H), 7.81 (d, 1H), 7.06 (d, 1H), 4.68 (d, 1H, *J* = 12), 4.22-4.38 (m, 1H), 4.05-4.12 (m, 1H), 3.93-4.20 (m, 1H), 3.78-3.91 (m, 1H), 1.28 (s, 9H).

<u>(±)-8-[2-(1-Carbethoxyprop-1-enyl)]-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (Structure **28** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2, R^6 = trifluoromethyl, R^{13} = CH_2CF_3, R^b = *t*-butyl)</u>: A solution of (±)-3,4-dihydro-8-(trifluoroacetyl)-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-

(trimethylacetamido)-2*H*-1,4-benzoxazine (40 mg, 0.08 mmol) and (carboxymethylene)triphenyl phosphorane (35 mg, 0.10 mmol) in 1 mL of dry toluene was heated at reflux for 5 h, whereupon the solvent was removed under reduced pressure to afford an oil. Flash chromatography (7:3 hexanes:EtOAc) afforded 18 mg (40%) of (±)-8-[2-(1-carbethoxyprop-1-enyl)]-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine. **^{1}H NMR** (400 MHz, $CDCl_3$) d 7.61 (d, 1H), 7.22 (s, 1H), 6.92 (d, 1H), 6.30 (s, 1H), 4.62-4.71 (m, 1H), 4.25-4.34 (m, 1H), 4.05-4.10 (m, 1H), 3.92-4.05 (m, 1H), 3.79-3.91 (m, 1H), 1.38 (t, 3H), 1.29 (s, 9H), 1.23 (q, 2H).

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **141**, Structure **29** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = trifluoromethyl, R^{13} = $-CH_2CF_3$): A solution of (±)-8-[2-(1-carbethoxyprop-1-enyl)]-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-7-(trimethylacetamido)-2*H*-1,4-benzoxazine (18 mg, 0.030 mmol) in 0.33 mL of acetic acid and 0.20 mL of concentrated hydrochloric acid was heated at reflux for 12 h. Ethyl acetate (10 mL) was added and the solution was neutralized with 6 N sodium hydroxide until the pH reached 7. The mixture was extracted with ethyl acetate (2 x 5 mL) and the combined organic layers were dried with anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give a greenish-brown oil. The crude product was purified *via* flash chromatography (1:1 hexanes EtOAc) to afford 6 mg (42%) of Compound **141**, a yellow solid. **^{1}H NMR** (400 MHz, CDCl3) δ11.4 (broad s, 1H), 7.21 (d, J = 9.2, 1H), 7.16 (s, 1H), 7.00 (d, J = 9.2, 1H), 4.78 (d, AB, J = 9.0, 1H), 4.29-4.38 (m, 1H), 4.05-4.11 (m, 1H), 3.90-4.05 (m, 1H), 3.83-3.93 (m, 1H).

EXAMPLE 43

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **142**, Structure **(–)-29** of **Scheme V**, where R^1, R^3, R^4, R^6, R^7, R^8 = H, R^2 = trifluoromethyl, R^5 = trifluoromethyl, R^{13} = $-CH_2CF_3$) and (+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **143**, Structure **(+)-29** of **Scheme V**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = trifluoromethyl, R^{13} = $-CH_2CF_3$)

Compound **141** (3 mg) was dissolved in hexanes:isopropanol was separated by chiral HPLC on a preparative Chiralpak AS column (20 x 250 mm) on a Beckman Gold HPLC with 14% ethanol:hexanes at a rate of 6.0 mL/min, to afford 1.2 mg each of Compound **142** and Compound **143**. Data for Compound **142**: HPLC (Chiralpak AS prep, 20 x 250 mm, 14% EtOH/hexanes, 6 mL/min) t_R 22.5 min; $[\alpha]_D = -20$ (c = 0.11, EtOH). Data for Compound **143**: HPLC (Chiralpak AS prep, 20 x 250 mm, 14% EtOH/hexanes, 6 mL/min) t_R 28.6 min; $[\alpha]_D = +15$ (c = 0.12, EtOH).

EXAMPLE 44

(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **144**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl)

(±)-6-Bromo-5-[(2'-*t*-butoxycarbonylamino)-(4',4',4'-trifluoro)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **7** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl): This compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.086 g, 0.24 mmol), (±)-2-*N*-*t*-butoxycarbonylamino-4,4,4-trifluoro-1-butanol (0.12 g, 0.49 mmol), triphenylphosphine (0.13 g, 0.49 mmol), DIAD (0.1 mL, 0.49 mmol) and *N*-methylmorpholine (0.09 mL) in THF (4 mL) to afford 0.061 g (43%) of (±)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-(4',4',4'-trifluoro)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline as a tan solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8, 1H),

7.58 (d, J = 9.3, 1H), 7.31 (s, 1H), 5.53 (m, 1H), 5.00 (bm, 1H), 4.41 (bm, 1H), 4.10 (bm, 2H), 2.74 (bm, 2H), 1.46 (bs, 9H), 1.42 (s, 3H), 1.41 (s, 3H).

<u>(±)-3,4-Dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl)</u>: This compound was prepared according to General Method 2 (EXAMPLE 1) from (±)-6-bromo-5-[(2'-*t*-butoxycarbonylamino)-(4',4',4'-trifluoro)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (0.061 g, 0.11 mmol) in CH_2Cl_2 (2 mL) and TFA (2 mL) to afford 0.038 g (75%) of (±)-6-bromo-5-[(2'-amino-(4',4',4'-trifluoro)-1'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, J = 9.3, 1H), 7.58 (d, J = 8.8, 1H), 7.32 (s, 1H), 5.53 (m, 1H), 3.91 (m, 2H), 3.85 (m, 1H), 2.57 (m, 1H), 2.24 (m, 1H), 1.65 (bs, 2H), 1.42 (d, J = 2.0, 3H), 1.41 (d, J = 1.5, 3H). This material (0.038g, 0.08 mmol) was carried on according to General Method 3 (EXAMPLE 1) by treatment with $Pd_2(dba)_3$ (1.5 mg), BINAP (2 mg) and *t*-BuONa (11 mg, 0.12 mmol) in toluene (1 mL) heated at reflux to afford 0.025 g (79%) of (±)-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, a yellow solid. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, J = 8.9, 1H), 7.20 (s, 1H), 7.04 (d, J = 8.9, 1H), 5.48 (m, 1H), 4.30 (dd, J = 10.7, 3.1, 1H), 4.11 (m, 2H), 3.95 (m, 1H), 2.41 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H).

<u>(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **144**, Structure **9** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl)</u>: Compound **144** was prepared according to General Method 4 (EXAMPLE 1) from (±)-3-ethyl-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (8 mg, 0.02 mmol) in conc. HCl (1 mL) in AcOH (1 mL) heated at 90°C to afford Compound **144**, a yellow solid. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ11.91 (bs, 1H), 7.14 (s, 1H), 6.94 (s, 2H), 4.31 (dd, J = 10.7, 2.4, 1H), 4.08 (m, 1H), 4.05 (bs, 1H), 3.92 (m, 1H), 2.38 (m, 2H).

EXAMPLE 45

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **145**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = CH_3)

(±)-3,4-Dihydro-8-isopropoxy-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = CH_3). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.025 g, 0.06 mmol), paraformaldehyde (0.02 g, 0.6 mmol) and $NaCNBH_3$ (0.04 g, 0.6 mmol) in 2 mL glacial acetic acid to afford 0.017 g (65%) of (±)-3-ethyl-3,4-dihydro-8-isopropoxy-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, of sufficient purity as to be used directly in the next reaction. ^{1}**H NMR** (500 MHz, $CDCl_3$) 7.48 (d, J = 8.8, 1H), 7.22 (d, J = 9.3, 1H), 7.21 (s, 1H), 5.49 (m, 1H), 4.37 (d, J = 10.7, 1H), 4.08 (d, J = 10.7, 1H), 3.68, (m, 1H), 3.05 (s, 3H), 2.40 (m, 2H), 1.39 (d, J = 6.3, 3H), 1.38 (d, J = 6.3, 3H).

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **145**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = CH_3): Compound **145** was prepared according to General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.017 g, 0.04 mmol) in conc. HCl (1.5 mL) in AcOH (1.5 mL) heated at 90°C to afford Compound **145,** a yellow solid. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 12.52 (bs, 1H), 7.16 (s, 1H), 7.06 (d, J = 9.3, 1H), 7.04 (d, J = 9.3, 1H), 4.38 (dd, J = 11.23, 2.0, 1H), 4.11 (d, J = 5.4, 1H), 3.67 (m, 1H), 3.00 (s, 3H), 2.38 (m, 2H).

EXAMPLE 46

(±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **146**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = Et)

(±)-4-Ethyl-3,4-Dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = Et): This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.019 g, 0.05 mmol) and $NaBH_4$ (0.5 pellets, >0.5 mmol) in 2 mL glacial acetic acid to afford (±)-4-ethyl-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, of sufficient purity as to be used directly in the next reaction.

(±)-3-Ethyl-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **146**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = Et): Compound **146** was prepared according to General Method 4 (EXAMPLE 1) from (±)-4-ethyl-3,4-dihydro-8-isopropoxy-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline in conc. HCl (2.5 mL) in AcOH (2.5 mL) heated at 90°C to afford Compound **146**, a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.97 (bs, 1H), 7.15 (s, 1H), 7.06 (d, *J* = 9.3, 1H), 7.01 (d, *J* = 8.8, 1H), 4.38 (dd, *J* = 1.0, 10.7, 1H), 3.88 (d, *J* = 11.2, 1H), 3.71 (m, 1H), 3.47 (m, 1H), 3.25 (m, 1H), 2.41 (m, 1H), 2.28 (m, 1H), 1.22 (t, *J* = 7.3, 3H).

EXAMPLE 47

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **147**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = 2,2,2-trifluoroethyl)

(±)-3,4-Dihydro-8-isopropoxy-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 =

trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = 2,2,2-trifluoroethyl): This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.02 g, 0.05 mmol) and $NaBH_4$ (0.5 pellets, >0.5 mmol) in 4 mL trifluoroacetic acid to afford 0.02 g (83%) of (±)-3,4-dihydro-8-isopropoxy-4-methyl-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, of sufficient purity as to be used directly in the next reaction.

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **147**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = 2,2,2-trifluoroethyl): Compound **147** was prepared according to General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (0.02 g, 0.04 mmol) in conc. HCl (2 mL) in AcOH (2 mL) heated at 90°C to afford 12 mg (67%) of Compound **147,** a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) 12.57 (bs, 1H), 7.18 (s, 1H), 7.17 (d, *J* = 8.8, 1H), 7.08 (d, *J* = 8.8, 1H), 4.44 (dd, *J* = 10.7, 1.0, 1H), 4.06 (m, 1H), 3.96 (m, 1H), 3.79 (m, 1H), 3.73 (m, 1H), 2.38 (m, 2H).

EXAMPLE 48

(-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **148**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = 2,2,2-trifluoroethyl), and (+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **149**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = 2,2,2-trifluoroethyl)

Compound **147** (12 mg) was dissolved in hexanes:ethanol was separated by chiral HPLC on a preparative Chirapak AS column (20 x 250 mm) on a Beckman Gold HPLC with 86% hexanes:ethanol at a rate of 7.0 mL/min, to afford 6 mg each of Compound **148** and Compound **149.** Data for Compound **148**: HPLC (Chirapak AS prep, 14% EtOH/hexanes, 7

mL/min) t_R 25.6; $[\alpha]_D$ = −35.9 (c = 0.30, EtOH). Data for Compound **149**: HPLC (Chiralpak AS prep, 20 x 250 mm, 14% EtOH/hexanes, 6 mL/min) t_R 64.1 min; $[\alpha]_D$ = +34.6 (c = 0.31, EtOH).

EXAMPLE 49

(±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **150**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = 2,2,2-trifluoroethyl, R^{13} = cyclopropylmethyl)

Compound **150** was prepared by General Method 5 (EXAMPLE 1) Compound **144** (0.02 g, 0.06 mmol), cyclopropylmethylcarboxaldehyde (0.05 mL, 0.6 mmol) and $NaCNBH_3$ (0.036 g, 0.6 mmol) in 1 mL glacial acetic acid and 3mL methanol to afford Compound **150**. **^{1}H NMR** (500 MHz, $CDCl_3$) 12.55 (bs, 1H), 7.20 (s, 1H), 7.17 (d, *J* = 8.6, 1H), 7.05 (d, *J* = 9.2, 1H), 4.41 (dd, *J* = 10.7, 1.2, 1H), 4.01 (d, *J* = 9.2, 1H), 3.89 (m, 1H), 3.35 (dd, *J* = 15.0, 6.1, 1H), 3.04 (dd, *J* = 14.7, 6.7, 1H), 2.34 (m, 2H), 1.04 (m, 1H), 0.61 (m, 2H), 0.25 (m, 2H).

EXAMPLE 50

(3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **151**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = ethyl, R^{13} = cyclopropylmethyl)

Compound **151** was prepared by General Method 5 (EXAMPLE 1) Compound **107** (0.015 g, 0.05 mmol), cyclopropylmethylcarboxaldehyde (0.05 mL, 0.5 mmol) and $NaCNBH_3$ (0.032 g, 0.5 mmol) in 1 mL glacial acetic acid and 3 mL methanol to afford Compound **151**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.23 (bs, 1H), 7.15 (d, *J* = 8.9, 1H), 7.13 (s, 1H), 6.98 (d, *J* = 8.9, 1H), 4.33 (dd, *J* = 10.4, 1.8, 1H), 3.96 (dd, *J* = 10.4, 2.4, 1H), 3.37 (dd, *J* = 14.6, 5.8, 1H), 3.34 (m, 1H), 3.00 (dd, *J* = 15.0, 7.0, 1H), 1.55 (m, 2H), 1.03 (m, 1H), 0.97 (t, *J* = 7.6, 3H), 0.57 (m, 2H), 0.23 (m, 2H).

EXAMPLE 51

(3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **152**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = isopropyl, R^{13} = 2-chloroethyl)

Compound **152** was prepared according to General Method 5 (EXAMPLE 2) from (3*R*)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (16 mg, 0.05 mmol) and $NaBH_4$ pellets (>10 equiv) in 0.5 g chloroacetic acid to afford 11 mg (58%) of (3*R*)-4-(2-chloroethyl)-3,4-dihydro-8-isopropoxy-3-isopropyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline. This material (11 mg, 0.03 mmol) was carried on according to General Method 4 (EXAMPLE 1) by treatment with 4 mL of 1:1 acetic acid:concentrated HCl (0.02M) heated at 90°C for 4 h to afford Compound **152**. **^{1}H NMR** (500 MHz, $CDCl_3$) 12.06 (bs, 1H), 7.13 (s, 1H), 7.12 (d, *J* = 8.8, 1H), 6.98 (d, *J* = 8.8, 1H), 4.53 (dd, *J* = 10.7, 1.5, 1H), 3.88 (dd, *J* = 10.7, 2.4, 1H), 3.82 (m, 1H), 3.71 (m, 1H), 3.63 (m, 1H), 3.49 (m, 1H), 2.93 (m, 1H), 1.82 (m, 1H), 0.99 (d, *J* = 10.3, 3H), 0.98 (d, *J* = 10.3, 3H).

EXAMPLE 52

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **153**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^3 = Me, R^{13} = CH_2CF_3)

(±)-6-Bromo-5-[(1'-*t*-butoxycarbonylamino)-2'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure 7 of **Scheme II**, where R^1, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^3 = Me): The compound was prepared according to General Method 1 (EXAMPLE 1) from 6-bromo-5-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (0.1 g, 0.3 mmol), (±)-1-*N*-t-butoxycarbonyl-2-propanol (80 mg, 0.5 mmol), triphenylphosphine (120 mg, 0.5 mmol) and diisopropyl azodicarboxylate (0.09 ml, 0.5 mmol) in 0.12 mL *N*-methylmorpholine in 3 mL dry THF to afford 145 mg (63%) of (±)-6-bromo-5-[(1'-*t*-butoxycarbonylamino)-2'-propoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline after flash

chromatography (4:1 hexanes/EtOAc). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 9.3, 1H), 7.51 (d, *J* = 8.8, 1H), 7.27 (s, 1H), 5.53 (m, 1H), 5.12 (m, 2H), 3.57 (m, 1H), 3.28 (m, 1H), 1.46 (s, 9H), 1.43 (d, *J* = 8.3, 3H), 1.42 (d, *J* = 8.3, 3H), 0.92 (d, *J* = 6.3, 3H).

<u>(±)-6-Bromo-5-(1'-amino-2'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline</u>: This compound was prepared according to General Method 2 (EXAMPLE 1) from (±)-6-bromo-5-[(3'-*t*-butoxycarbonylamino)-2'-butoxy]-2-isopropoxy-4-(trifluoromethyl)quinoline (91 mg, 0.2 mmol) in 2 mL CH_2Cl_2 and 2 mL TFA to afford 86 mg (100%) of (±)-6-bromo-5-(1'-amino-2'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline. ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8, 1H), 7.53 (d, *J* = 8.8, 1H), 7.27 (s, 1H), 5.52 (m, 1H), 5.21 (m, 1H), 3.20 (m, 2H), 1.42 (d, *J* = 10.3, 3H), 1.41 (d, *J* = 10.3, 3H), 0.93 (d, *J* = 6.3, 3H).

<u>(±)-3,4-Dihydro-8-isopropoxy-2-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **8** of **Scheme II**, where R^1, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^3 = Me)</u>: This compound was prepared according to General Method 3 (EXAMPLE 1) from (±)-6-bromo-5-(1'-amino-2'-propoxy)-2-isopropoxy-4-(trifluoromethyl)quinoline (86 mg, 0.2 mmol), (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (5 mg), $Pd_2(dba)_3$ (4 mg), sodium *t*-butoxide (28 mg, 0.3 mmol) to afford 9 mg (14%) of (±)-3,4-dihydro-8-isopropoxy-2-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, after purification by flash chromatography (4:1 hexanes:EtOAc). ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.8, 1H), 7.18 (s, 1H), 7.04 (d, *J* = 8.8, 1H), 5.48 (m, 1H), 4.23 (m, 1H), 3.82 (m, 1H), 3.47 (dd, *J* = 11.7, 2.4, 1H), 3.22 (dd, *J* = 11.2, 8.3, 1H), 1.44 (d, *J* = 6.3, 3H), 1.39 (d, *J* = 6.3, 3H), 1.38 (d, *J* = 6.3, 3H).

<u>(±)-3,4-Dihydro-8-isopropoxy-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (Structure **10** of **Scheme II**, where R^1, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^3 = Me, R^{13} = CH_2CF_3)</u>: This compound was prepared according to General Method 6 (EXAMPLE 3) from (±)-3,4-dihydro-8-isopropoxy-2-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (9 mg, 0.03 mmol) and $NaBH_4$ pellets (>10 equiv) in 1 mL trifluoroacetic acid to afford 8 mg (73%) of (±)-3,4-dihydro-8-isopropoxy-2-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline, which was carried on without purification.

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **153**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, R^6, = H, R^2 = trifluoromethyl, R^3 = Me, R^{13} = CH_2CF_3):

Compound **153** was prepared by General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-8-isopropoxy-2-methyl-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (8 mg, 0.02 mmol) in 4 mL of a 1:1 acetic acid:concentrated HCl heated at 90°C for 4 h to afford Compound **153**. **^{1}H NMR** (500 MHz, $CDCl_3$) 11.68 (bs, 1H), 7.14 (s, 1H), 7.08 (d, J = 8.8, 1H), 6.94 (d, J = 9.3, 1H), 4.24 (m, 1H), 3.88 (m, 1H), 3.78 (m, 1H), 3.44 (dd, J = 11.7, 2.4, 1H), 3.29 (dd, J = 11.7, 8.8, 1H), 1.45 (d, J = 6.3, 3H).

EXAMPLE 53

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound 154, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = isopropyl, R^{13} = 2-hydroxy-2-methylpropyl)

(3*R*)-3-Ethyl-4-(2-methyl-2-propenyl)-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline: This compound was prepared by treatment of (3*R*)-3-ethyl-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (20 mg, 0.059 mmol), 2-methallyl bromide (40 mg, 0.30 mmol) and K_2CO_3 (41 mg, 0.30 mmol) in 1 mL DMF heated at 50 °C for 16 h. The reaction was treated with an additional 2-methallyl bromide (60 mg) and was heated overnight at 50 °C. The mixture was extracted with ethyl acetate (2 x 25 mL), and the combined organic layers were washed with water (25 mL), brine (25 mL), dried over $MgSO_4$, filtered, and concentrated afford 20 mg (87 %) of (3*R*)-3-ethyl-4-(2-methyl-2-propenyl)-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline after flash chromatography (9:1 hexanes:EtOAc). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (d, J = 9.0, 1H), 7.18 (s, 1H), 7.12 (d, J = 9.0, 1H), 5.47 (septet, J = 6.2, 1H), 4.91 (broad s, 2H), 4.33 (dd, J = 10.7, 2.1, 1H), 3.96 (dd, J = 10.7, 2.6, 1H), 3.85 (d, *AB*, J = 17.1, 1H), 3.80 (d, *AB*, J = 17.1, 1H), 3.20-3.26 (m, 1H), 1.79 (s, 3H), 1.58-1.68 (m, 2H), 1.38 (d, J = 6.2, 3H), 1.37 (d, J = 6.2, 3H), 0.96 (t, J = 7.4, 3H).

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **154**, Structure **11** of **Scheme II**, where R^1, R^3, R^4, R^5, = H, R^2 = trifluoromethyl, R^6 = isopropyl, R^{13} = 2-hydroxy-2-methylpropyl): This compound was prepared by General Method 4 (EXAMPLE 1) with some modifications. A solution of (3*R*)-3-ethyl-4-(2-methyl-2-propenyl)-3,4-dihydro-8-isopropoxy-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline (11 mg, 0.028 mmol) was heated in 1 mL concentrated HCl at 75 °C and afforded 3 mg (30%) of Compound **154** after sequential column chromatography (9:1 CH_2Cl_2:MeOH) and preparative HPLC (ODS semi-prep column, 20 x 250 mm, 65% MeOH/water, 3 mL/min). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.4 (broad s, 1H), 7.26 (d, *J* = 8.9, 1H), 7.10 (s, 1H), 6.86 (d, *J* = 8.9, 1H), 4.40 (d, *J* = 10.3, 1H), 4.06 (broad d, *J* = 10.3, 1H), 3.29 (d, *AB*, *J* = 15.0, 1H), 3.20-3.30 (m, 1H), 3.10 (d, *AB*, *J* = 15.0, 1H), 1.99 (s, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 0.97 (t, *J* = 7.4, 3H).

EXAMPLE 54

(3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one (Compound **155**, Structure **17** of **Scheme III**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = isobutyl, R^{13} = CH_2CF_3)

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol (Structure **21** of **Scheme V**, where R^3, R^4, R^5, R^5, R^7, R^8 = H, R^6 = isobutyl): This compound was prepared according to the procedure described in EXAMPLE 41 (Structure **21** of **Scheme V**) from 3,4-difluoronitrobenzene (8.73 g, 54.9 mmol), *R*-2-amino-4-methyl-1-pentanol (5.00 g, 42.7 mmol) in EtOH heated at reflux for 16 h to afford 6.0 g (55%) of (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol, a yellow solid, after flash chromatography (gradient elution, hexanes:EtOAc 9:1 to 1:1). Data for (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol: R_f 0.3 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 1H), 7.90 (dd, 1H, *J* = 11.7, 2.7), 6.74 (dd, 1H, *J* = 8.6, 8.6), 4.62-4.57 (m, 1H), 3.82-3.74 (m, 1H), 3.75-3.62 (m, 2H), 1.77-1.65 (m, 1H), 1.61-1.45 (m, 2H), 0.99 (d, 3H, *J* = 6.6), 0.93 (d, 3H, *J* = 6.6).

<u>(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-isobutyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **22** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = isobutyl, R^A = trifluoromethyl)</u>: This compound was prepared according to the procedure described in EXAMPLE 41 (Structure **22** of **Scheme V**) from (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol (6.0 g, 23 mmol) trifluoroacetaldehyde ethyl hemiacetal (30.4 g, 211 mmol) and *p*-toluenesulfonic acid (0.020 g, 0.10 mmol) in 250 mL benzene to afford 5.15 g (65%) of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine. Data for (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine as a mixture of diastereomers: R_f 0.8 (3:1 hexanes:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 8.03-7.94 (m, 2H), 6.96-6.88 (m, 1H), 5.81 (q, 1H, minor diast., *J* = 4.7), 5.69 (q, 1H, major diast., *J* = 4.7), 4.45-4.40 (m, 1H, minor diast.), 4.36-4.28 (m, 1H, major diast.), 4.11-4.01 (m, 2H), 1.82-1.74 (m, 1H), 1.66-1.52 (m, 2H), 1.02 (d, 3H, major diast., *J* = 6.4), 0.99-0.95 (m, 3H), 0.91 (d, 3H, minor diast., *J* = 6.6).

<u>(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol (Structure 23 of Scheme V, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = isobutyl, R^{13} = CH_2CF_3)</u>: To a solution of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine (4.8 g, 14.3 mmol) and Et_3SiH (21.6 g, 186 mmol) in 60 mL chloroform was added BF_3OEt_2 (14.2, 60 mmol, added in portions) The reaction was heated at reflux for 1 d After cooling, the reaction was poured in water (200 mL) and extracted with chloroform (3 x 150 mL). The organic layers were combined, washed sequentially with water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil. Flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 3:1) afforded 2.1 g (44%) of (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol, an orange oil. Data for (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol: R_f 0.8 (3:1 hexanes:EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dd, 1H, *J* = 9.3, 2.4), 7.94 (dd, 1H, *J* = 12.9, 2.5), 7.40 (dd, 1H, *J* = 8.7, 8.7), 4.21-4.10 (m, 1H), 3.89-3.78 (m, 1H), 3.79-3.65 (m, 3H), 1.96-1.89 (m, 1H), 1.67-1.54 (m, 1H), 1.55-1.44 (m, 1H), 1.32-1.22 (m , 1H), 0.91 (d, 3H, *J* = 6.6), 0.77 (d, 3H, *J* = 6.6).

(3R)-3,4-Dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazine (Structure **24** of **Scheme V**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = isobutyl, R^{13} = CH_2CF_3): This compound was prepared according to the procedure described in EXAMPLE 41 (Structure **24** of **Scheme V**) from (2R)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol (1.95 g, 5.76 mmol) in 30 mL THF and NaH (1.4 g, 35 mmol) in 25 mL THF heated at reflux for 1 hr to afford 0.87 g (50%) of (3R)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazine, a yellow oil. Data for (3R)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazine: R_f 0.6 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dd, 1H, J = 9.1, 2.7), 7.71 (d, 1H, J = 2.5), 6.72 (d, 1H, J = 9.1), 4.30 (dd, 1H, ABx, J = 11.0, 1.5), 4.19-4.06 (m, 1H), 4.06-4.01 (m, 1H), 3.82-3.73 (m, 1H), 3.53-3.47 (m, 1H), 1.71-1.61 (m, 2H), 1.38-1.29 (m, 1H), 0.99 (d, 3H, J = 6.5), 0.96 (d, 3H, J = 6.5).

(3R)-7-Amino-3,4-dihydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazine (Structure **16** of **Scheme III**, where R^3, R^4, R^5, R^7, R^8 = H, R^6 = isobutyl, R^{13} = CH_2CF_3): This compound was prepared by treatment of (3R)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2H-1,4-benzoxazine (0.22 g, 0.69 mmol) and 10% Pd/C (0.075 g) in 5 mL ethyl acetate under an H_2 atmosphere for 16 h. The mixture was filtered through Celite and concentrated to an oil. Flash chromatography (3:1 hexanes:ethyl acetate) afforded 0.13 g (65%) of (3R)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2H-1,4–benzoxazine. Data for (3R)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2H-1,4–benzoxazine: R_f 0.3 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 (d, 1H, J = 8.5), 6.27 (dd, 1H, J = 8.5, 2.6), 6.23 (d, 1H, J = 2.5), 4.10 (dd, 1H, ABx, J = 10.6, 1.8), 3.97 (dd, 1H, ABx, J = 10.6, 2.3), 3.70-3.51 (m, 2H), 3.38 (broad s, 2H), 3.19-3.13 (m, 1H), 1.75-1.63 (m, 1H), 1.47-1.25 (m, 2H), 0.93 (d, 3H, J = 6.6), 0.89 (d, 3H, J = 6.6).

(3R)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8H-[1,4]oxazino[2,3-f]quinolin-8-one (Compound **155**, Structure **17** of **Scheme III**, where R^1, R^3, R^4, R^5, R^7, R^8 = H, R^2 = trifluoromethyl, R^6 = isobutyl, R^{13} = CH_2CF_3), and (2R)-1,2,3,6-tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one (Structure **18** of **Scheme III**, where R^1, R^3, R^4, R^5, R^7 = H, R^2 =

trifluoromethyl, R^6 = isobutyl, R^{13} = CH_2CF_3): This compound was prepared by treatment of (3*R*)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2*H*-1,4–benzoxazine (0.13 g, 0.45 mmol) and ethyl-4,4,4-trifluoroacetoacetate (0.25 g, 1.4 mmol) in 6 mL toluene heated at reflux for 3h, followed by removal of solvent and treatment with 3 mL concentrated H_2SO_4 heated to 95 ^{0}C for 1 h. The mixture was poured into water (100 mL), neutralized with 6N NaOH, and extracted with chloroform (3 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The baseline impurities and were removed and partial purification achieved by flash chromatography (95:5 CH_2Cl_2:MeOH). Further purification by HPLC (Kromasil, 0.5" semi-prep column, 70% MeOH/water at 3 mL/min) afforded 5.0 mg (3%) of Compound **155**, and recrystallization of the other impure fractions (ethyl acetate:hexanes) afforded 17 mg (9%) of (2*R*)-1,2,3,6-tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one, the regioisomer of Compound **155**. Data for Compound **155**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.0-12.4 (v broad s, 1H), 7.15 (s, 1H), 7.13 (d, *J* = 9.0, 1H), 7.01 (d, *J* = 9.0, 1H), 4.34 (d, *J* = 11, 1H), 3.99 (broad d, *J* = 10, 1H), 3.75-3.85 (m, 1H), 3.65-3.75 (m, 1H), 3.35-3.40 (m, 1H), 1.70-1.80 (m, 1H), 1.40-1.50 (m, 1H), 1.30-1.40 (m, 1H), 0.95 (d, *J* = 6.5, 3H), 0.93 (d, *J* = 7.0, 3H).

BIOLOGICAL EXAMPLES

A. Steroid Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is incorporated by reference herein, the compounds of the present invention were tested and found to have strong, specific activity as agonists, partial agonists and antagonists of AR. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

The co-transfection assay provides a method for identifying functional agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native hormones and quantifying their activity for responsive IR proteins. In this regard, the co-transfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, *e.g.*, T. Berger et al. 41 *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein incorporated by reference.

In the co-transfection assay, a cloned cDNA for an IR (*e.g.*, human PR, AR or GR) under the control of a constitutive promoter (*e.g.*, the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to make the IR protein of interest. A second gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor and its native hormone.

The co-transfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, *e.g.*, by increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter transcription. A partial agonist's activity can be detected in a manner similar to that of the full agonist, except that the maximum measured activity, *e.g.*, luciferase production, is less than that of an agonist standard. For example, for AR, a partial agonist can be detected by measuring increased luciferase production, but the maximum effect at high concentration is less than the maximum effect for dihydrotestosterone. To detect antagonists, the co-

transfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (*e.g.*, progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (*e.g.*, luciferase production). The co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the co-transfection assay and in standard IR binding assays, according to the following illustrative Examples.

B. Co-transfection assay

CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum (CH-FBS) then transferred to 96-well microtiter plates one day prior to transfection.

To determine AR agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by calcium phosphate coprecipitation according to the procedure of Berger et al., 41 *J. Steroid Biochem. Mol. Biol.*, 733 (1992) with the following plasmids: pRShAR (5 ng/well), MTV-LUC reporter (100 ng/well), pRS-ß-Gal (50 ng/well) and filler DNA (pGEM; 45 ng/well). The receptor plasmid, pRShAR, contains the human AR under constitutive control of the SV-40 promoter, as more fully described in J.A. Simental et al., "Transcriptional activation and nuclear targeting signals of the human androgen receptor", 266 *J. Biol. Chem.*, 510 (1991).

The reporter plasmid, MTV-LUC, contains the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MTV) long terminal repeat, a conditional promoter containing an androgen response element. See *e.g.*, Berger et al. supra. In addition,

pRS-ß-Gal, coding for constitutive expression of E. coli ß-galactosidase (ß-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (*i.e.* progesterone as a PR agonist, mifepristone ((11β,17β)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one: RU486; Roussel Uclaf) as a PR antagonist; dihydrotestosterone (DHT; Sigma Chemical) as an AR agonist and 2-OH-flutamide (the active metabolite of 2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]-pronanamide; Schering-Plough) as an AR antagonist; estradiol (Sigma) as an ER agonist and ICI 164,384 (N-butyl-3,17-dihydroxy-*N*-methyl-(7-α,17-β)-estra-1,3,5(10)-triene-7-undecanamide; ICI Americas) as an ER antagonist; dexamethasone (Sigma) as a GR agonist and RU486 as a GR antagonist; and aldosterone (Sigma) as a MR agonist and spironolactone ((7-α-[acetylthio]-17-α-hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ-lactone (Sigma) as an MR antagonist; and/or the modulator compounds of the present invention in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and ß-Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

LUC response/ß-Gal rate

where ß-Gal rate = ß-Gal/ß-Gal incubation time.

The mean and standard error of the mean (SEM) of the NR were calculated. Data were plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist for PR, AR, ER, GR or MR. Antagonist activity was determined by testing the

amount of LUC expression in the presence of a fixed amount of DHT as an AR agonist and progesterone as a PR agonist at the EC_{50} concentration. The concentration of a test compound that inhibited 50% of LUC expression induced by the reference agonist was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

Table 1: Agonist, partial agonist, antagonist and binding activity of androgen receptor modulator compounds of present invention and the reference agonist compound, dihydrotestosterone (**DHT**), a known synthetic androgen, fluoxymesterone (**Fluox**) and reference antagonist compounds, 2-hydroxyflutamide (**Flut**) and Casodex (**Cas**), on hAR in CV-1 cells. Efficacy (%) for AR agonist is determined by comparing activity (*e.g.*, luciferase production) of putative agonist to that of dihydrotestosterone (**DHT**). Efficacy (%) for AR antagonist is determined by the percentage amount by which the luciferase production is reduced (maximum concentration of antagonist) from the luciferase production of the standard (**DHT**).

Cmpd	**AR Agonist CV-1 Cells**		**AR Antagonist CV-1 Cells**	
No.	**Efficacy (%)**	**Potency (nM)**	**Efficacy (%)**	**Potency (nM)**
101	na	na	64	72
102	na	na	32	nd
103	37	304	24	nd
104	73	7	na	na
106	97	228	na	na
107	17	301	56	70
109	29	411	na	na
110	89	0.6	na	na
114	74	53	na	na
116	na	na	79	65
117	na	na	74	8
122	76	270	na	na
124	70	2	na	na
126	78	35	na	na
128	na	na	88	50
135	72	11	na	na
136	61	34	24	nd
138	na	na	90	613
DHT	100	6	na	na
Fluox	120	2.8	na	na
Flut	na	na	83	25
Cas	na	na	81	201

[1] na = not active (i.e. efficacy of <20 and potency of >10,000 nM for the cotransfection assay and K_i > 1000 nM for the binding assay)
nd = not determined

Table 2: Overall agonist and antagonist potency of selected androgen receptor modulator compounds of present invention and the reference agonist and antagonist compounds shown in Table 1 on PR, AR, ER, GR and MR.

Cmpd	PR Potency		AR-wt Potency		ER Potency		GR Potency	MR Potency
No.	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Antag (nM)	Antag (nM)
101	na	3900	na	72	na	na	na	na
103	na	3150	304	nd	na	na	na	na
110	na	520	0.6	na	na	na	1510	1270
114	na	700	53	na	na	na	5900	na
124	na	360	2	na	na	na	2400	na
135	na	481	11	na	na	na	2500	na
Fluox	1210	224	2.8	na	na	na	263	193
Prog	4	na	1300	na	na	na	na	nt
RU486	na	0.1	na	12	na	1500	0.7	1100
DHT	na	1800	6	na	1700	na	na	nt
Flut	na	1900	na	26	na	na	na	na
Estr	nt	nt	na	na	7	na	na	nt
ICI 164	na	na	na	na	na	160	na	na
Spir	nt	268	nt	nt	na	na	2000	25

na = not active (i.e., efficacy of >20 and potency of >10,000); nd = not determined, nt = not tested

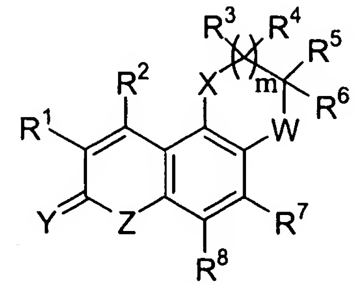
The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

While in accordance with the patent statutes, description of the various embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented by way of example.

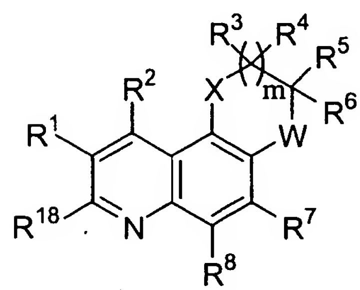
We claim:

1. A compound having the formula:



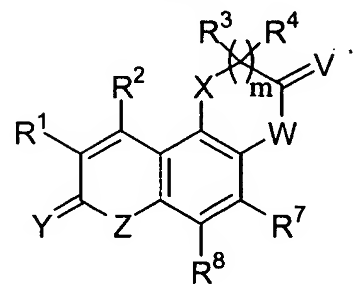
(I)

OR



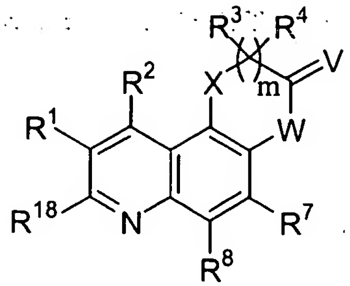
(II)

OR



(III)

OR



(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^9 is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{10} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$, wherein the

alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{11} and R^{12} each independently is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{13} is selected from the group of $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

R^{16} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{17} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{16}R^{17}$, SOR^{17} and SO_2R^{17}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{19} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is selected from the group of O, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^1 is selected from the group of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

3. A compound according to claim 2, wherein R^1 is selected from the group of hydrogen, F, Cl, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

4. A compound according to claim 3, wherein R^1 is selected from the group of hydrogen, F and optionally substituted C_1-C_4 alkyl.

5. A compound according to claim 1, wherein R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 heteroalkyl, C_2-C_6 alkynyl and C_2-C_6 alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted.

6. A compound according to claim 5, wherein R^2 is selected from the group of hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

7. A compound according to claim 6, wherein R^2 is selected from the group of hydrogen, $C_1 - C_2$ alkyl, $C_1 - C_2$ haloalkyl and $C_1 - C_2$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

8. A compound according to claim 7, wherein R^2 is CF_3.

9. A compound according to claim 1, wherein

R^3 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

10. A compound according to claim 9, wherein R^3 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic ring.

11. A compound according to claim 9, wherein R^3 is selected from the group of hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

12. A compound according to claim 1, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted.

13. A compound according to claim 12, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl,

$C_2 - C_4$ alkynyl and $C_2 - C_4$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, alkynyl and alkenyl groups may be optionally substituted.

14. A compound according to claim 13, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

15. A compound according to claim 12, wherein R^6 is selected from the group of aryl, arylalkyl and heteroaryl, wherein the aryl, arylalkyl and heteroaryl groups may be optionally substituted.

16. A compound according to claim 1, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl, $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted.

17. A compound according to claim 16, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

18. A compound according to claim 17, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

19. A compound according to claim 18, wherein R^5 is hydrogen or CF_3.

20. A compound according to claim 1, wherein R^7 is selected from the group of hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted.

21. A compound according to claim 1, wherein R^8 is selected from the group of hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted

22. A compound according to claim 21, wherein R^7 and R^8 are each hydrogen or optionally substituted $C_1 - C_2$ alkyl.

23. A compound according to claim 1, wherein R^9 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

24. A compound according to claim 23, wherein R^9 is selected from the group of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

25. A compound according to claim 1, wherein R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

26. A compound according to claim 25, wherein R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$ and CO_2R^{12}.

27. A compound according to claim 1, wherein R^4 is selected from the group of hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

28. A compound according to claim 27, wherein R^4 is selected from the group of hydrogen and optionally substituted $C_1 - C_2$ alkyl.

29. A compound according to claim 1, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_6$ alkyl, $C_3 - C_6$ cycloalkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkenyl, $C_2 - C_6$ alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, cycloalkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

30. A compound according to claim 29, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, $C_2 - C_4$ alkenyl and aryl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and aryl groups may be optionally substituted; or

R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring.

31. A compound according to claim 30, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

32. A compound according to claim 1, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

33. A compound according to claim 32, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16} and $NR^{16}R^{17}$.

34. A compound according to claim 33, wherein R^{18} is selected from the group of hydrogen, F, Cl and OR^{16}.

35. A compound according to claim 1, wherein R^{19} is selected from the group of hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

36. A compound according to claim 35, wherein R^{19} is selected from the group of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

37. A compound according to claim 1, wherein m is 0 or 1.

38. A compound according to claim 37, wherein m is 1.

39. A compound according to claim 1, wherein W is selected from the group of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$.

40. A compound according to claim 39, wherein W is NH or $N\{R^{13}\}$.

41. A compound according to claim 1, wherein X is selected from the group of O, S, NH and N{R^{11}}.

42. A compound according to claim 41, wherein X is O or S.

43. A compound according to claim 1, wherein Y is O or S.

44. A compound according to claim 43, wherein Y is O.

45. A compound according to claim 1, wherein Z is selected from the group of NH, N{R^{11}} and O.

46. A compound according to claim 45, wherein Z is NH or N{R^{11}}.

47. A compound according to claim 1, wherein V is S.

48. A compound according to claim 1, wherein V is O.

49. A compound according to claim 1, wherein:

R^1 is selected from the group of hydrogen, F, Cl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted

R^3 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring;

R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted;

R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

50. A compound according to claim 49, wherein:

R^7 is selected from the group of hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^8 is selected from the group of hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_3 - C_6$ cycloalkyl, $C_2 - C_6$ alkenyl, $C_2 - C_6$ alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl groups may be optionally substituted; or

R^6 and R^{13} taken together form a five to seven-membered saturated or unsaturated heterocyclic ring; and

R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl, heteroalkyl groups may be optionally substituted.

51. A compound according to claim 50, wherein:

m is 0 or 1;

W is selected from the group of NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}};

X is selected from the group of O, S, NH and N{R^{11}};

Y is O or S; and

Z is selected from the group of NH, N{R^{11}} and O.

52. A compound according to claim 1, wherein said compound is represented by formula (I).

53. A compound according to claim 1, wherein said compound is represented by formula (II).

54. A compound according to claim 1, wherein said compound is represented by formula (III).

55. A compound according to claim 1, wherein said compound is represented by formula (IV).

56. A compound according to claim 1, wherein said compound is selected from the group of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one ;

(3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-4-Ethyl-2,3,4,7-tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(6a*R*)-6a,7,8,9 -Tetrahydro-4-(trifluoromethyl)-1*H*,6*H*-pyrrolo[1',2':4,5][1,4]oxazino[2,3-*f*]quinolin-2-one;

2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-8-Chloro-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(3*R*) -3-Ethyl-3,4-dihydro-8-isopropoxy-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

(3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one.

57. A compound according to claim 1, wherein said compound is selected from the group of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

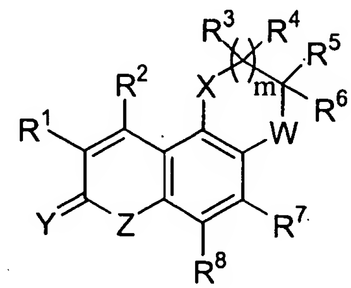
(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(−)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

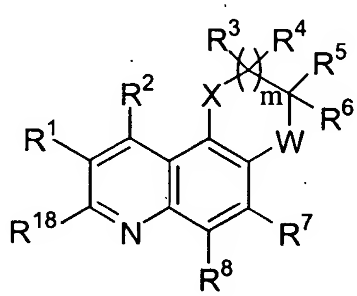
(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one.

58. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



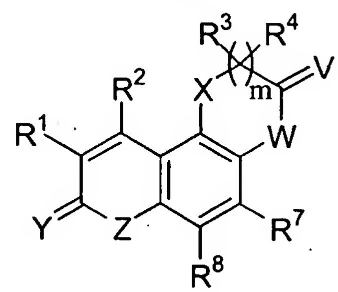
(I)

OR



(II)

OR



(III)

OR

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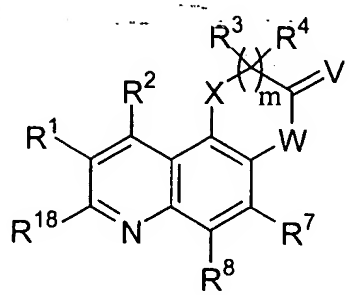

(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted;

R^9 is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{10} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$, wherein the

alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{11} and R^{12} each independently is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{13} is selected from the group of $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

R^{16} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{17} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{16}R^{17}$, SOR^{17} and SO_2R^{17}, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;

R^{19} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is selected from the group of O, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$;

and pharmaceutically acceptable salts thereof.

59. A pharmaceutical composition according to claim 58, wherein said composition is suitable for enteral, parenteral, suppository or topical administration.

60. A pharmaceutical composition according to claim 58, wherein R^1 is selected from the group of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

61. A pharmaceutical composition according to claim 1, wherein R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted.

62. A pharmaceutical composition according to claim 59, wherein

R^1 is selected from the group of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl; and

R^2 is selected from the group of hydrogen, $C_1 - C_2$ alkyl, $C_1 - C_2$ haloalkyl and $C_1 - C_2$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

63. A pharmaceutical composition according to claim 58, wherein R^3 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$

and $C(Y)NR^{10}R^{11}$; wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

64. A pharmaceutical composition according to claim 58, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted.

65. A pharmaceutical composition according to claim 64, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl, $C_1 - C_4$ heteroalkyl, $C_2 - C_4$ alkynyl and $C_2 - C_4$ alkenyl, wherein the alkyl, heteroalkyl, haloalkyl, alkynyl and alkenyl groups may be optionally substituted.

66. A pharmaceutical composition according to claim 58, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkynyl and $C_2 - C_6$ alkenyl, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted.

67. A pharmaceutical composition according to claim 66, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

68. A pharmaceutical composition according to claim 58, wherein R^7 and R^8 each independently is selected from the group of hydrogen, F, Cl, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl

and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

69. A pharmaceutical composition according to claim 58, wherein

R^9 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted; and

R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl and $C_1 - C_6$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

70. A pharmaceutical composition according to claim 58, wherein R^4 is selected from the group of hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

71. A pharmaceutical composition according to claim 58, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, $C_2 - C_6$ alkenyl, $C_2 - C_6$ alkynyl, $C_3 - C_6$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

72. A pharmaceutical composition according to claim 71, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

73. A pharmaceutical composition according to claim 58, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

74. A pharmaceutical composition according to claim 58, wherein R^{19} is selected from the group of hydrogen, $C_1 - C_4$ alkyl, $C_1 - C_4$ haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted.

75. A pharmaceutical composition according to claim 58, wherein m is 0 or 1.

76. A pharmaceutical composition according to claim 58, wherein
W is selected from the group of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$; and
X is selected from the group of O, S, NH and $N\{R^{11}\}$.

77. A pharmaceutical composition according to claim 58, wherein
Y is O or S; and
Z is selected from the group of NH, $N\{R^{11}\}$ and O.

78. A method of determining the presence of an androgen receptor (AR) in a cell or cell extract comprising: (a) labeling a compound according to any one of claims 1, 56 or 57; (b) contacting the cell or cell extract with said labeled compound; and (c) testing the contacted cell or cell extract to determine the presence of AR.

79. A method for purifying a sample containing an androgen receptor *in vitro*, comprising: (a) contacting said sample with a compound according to any one of claims 1, 56 or 57; (b) allowing said compound to bind to said androgen receptor to form a bound compound/receptor combination; and (c) isolating said bound compound/receptor combination.

80. A method of treating an individual having a condition mediated by an androgen receptor comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 56, or 57.

81. A method according to claim 80, wherein said compound is represented by formula (I).

82. A method according to claim 80, wherein said compound is represented by formula (II).

83. A method according to claim 80, wherein said compound is represented by formula (III).

84. A method according to claim 80, wherein said compound is represented by formula (IV).

85. A method according to claim 80, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, and hormone-dependent cancers.

86. A method according to claim 80, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

87. A method of modulating an androgen receptor in an individual comprising administering to said individual an androgen receptor modulating effective amount of a compound according to any one of claims 1, 56, or 57.

88. A method according to claim 87, wherein said individual has a condition mediated by an androgen receptor.

89. A method according to claim 87, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

90. A method according to claim 87, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

91. A method according to claim 87, wherein said modulation is activation.

92. A method according to claim 91, wherein said individual has a condition mediated by an androgen receptor.

93. A method according to claim 92, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases,

hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

94. A method according to claim 92, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

95. A method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 100 nM.

96. A method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 50 nM.

97. A method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 20 nM.

98. A method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 10 nM.

99. A method according to claim 87, wherein said modulation is inhibition.

100. A method according to claim 99, wherein said individual has a condition mediated by an androgen receptor.

101. A method according to claim 100, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

101. A method according to claim 100, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

103. A method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 100 nM.

104. A method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 50 nM.

105. A method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 20 nM.

106. A method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 10 nM.

107. A method of treating cancer, comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to any one of claims 1, 56 or 57.

ABSTRACT

Novel non-steroidal tricyclic quinolinone and tricyclic quinoline compounds and compositions that are agonists, partial agonists and/or antagonists for androgen receptors (AR), their preparation and their uses are described.

Applicant is respectfully requested to supply an amended declaration because the handwritten alterations to the oath by inventor Caferro were not properly initialed and dated.

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. §1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

In claim **46**, the term "claim **45**" was amended to read
-- claim **1** --.

In claim **56** at line 108, the term -- and -- was added at the end of the line.

In claim **56** at line 111, the term "a pharmaceutically acceptable salt" was amended to read -- pharmaceutically acceptable salts --.

In claim **57** at line 25, the term -- and -- was added at the end of the line.

In claim **57** at line 28, the term "a pharmaceutically acceptable salt" was amended to read -- pharmaceutically acceptable salts --.

In claim **58** at line 67, the entire line was deleted in favor of the term -- m is 1; --.

Claim **75** was cancelled.

In claim **108** at line 4, the term "and o" was amended to read
-- and --.

Authorization for this Examiner's Amendment was given in a telephone interview with Frank Miskiel on August 21, 2006

Papers related to this application may be submitted to Group 1600 via facsimile transmission (FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX (unofficially) directly to Examiner's computer is 571-273-0651. The telephone number for sending an Official FAX to the PTO is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ms. S. Anna Jiang, can be reached at **571-272-0627**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

All Post-Allowance Correspondence concerning this application must be mailed to:

BOX ISSUE FEE
COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

OR you can FAX them to the Office of Patent Publications at 571-273-8300, in order to expedite the handling of such correspondence as amendments under 37 C.F.R. §1.312; Information Disclosure Statements (IDS's), and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at **571-272-4200**. The Notice of Allowance also has an insert containing contact information for other items, including Issue Fees, receipt of formal drawings, and the status of the application.

LECrane:lec
08/23/2006

L. E. Crane, Ph.D. Esq.
Primary Patent Examiner
Technology Center 1600

Attorney's Docket No.: 18202-018001 / 1082

RESPONSE UNDER 37 CFR §1.116
– EXPEDITED PROCEDURE –
EXAMINING GROUP 1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Lin Zhi *et al.*	Art Unit :	1623
Serial No. :	10/080,503	Examiner :	Lawrence E. Crane, Ph.D.
Filed :	February 22, 2002		
Title :	**TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHOD**		

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE AFTER FINAL

Dear Sir:

Responsive to the Final Office Action, mailed January 25, 2006, entry and consideration of the following amendments and remarks are respectfully requested. It is respectfully submitted that the amendments and arguments presented below either place the application into condition for allowance or reduce the number of issues for appeal. For example, claims 1 and 58 are amended to define the substituents of the optionally substituted groups, obviating the rejections under 35 U.S.C. 112, first and second paragraphs. Claims 1 and 58 also are amended to separate the substituents for variables X and Z, as suggested by the Examiner in the rejection under 35 U.S.C. 112, first paragraph. Claims 1, 9, 29-31, 49, 50, 58, 63, 71 and 72 are amended to cancel subject matter directed to substituents that when taken together form a carbocyclic or heterocyclic ring, obviating the rejection under 35 U.S.C. 112, first paragraph.

Amendments to the claims are reflected in the listing of the claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 22 of this paper.

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I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop AF, Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

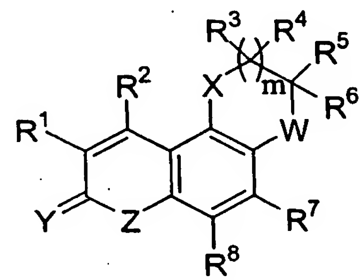
Stephanie Seidman

AMENDMENTS TO THE CLAIMS:

Claims 1-9, 11-31, 37-40, 46, 49-51, 56-72, 75-77 and 108 are pending. Claims 10, 41, 42 and 45 are cancelled herein without prejudice or disclaimer. Please amend claims 1, 9, 29-31, 49-51, 58, 63, 71, 72, 76 and 77 as indicated. New claim 108 is added herein. This listing of claims will replace all prior versions, and listings of claims, in the application.

LISTING OF CLAIMS:

1. (Currently amended) A compound having the formula:



(I)

wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^3 and R^4 each independently is selected from the group consisting of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; ~~or~~

~~R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or~~

~~R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;~~

R^5 and R^6 each independently is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; ~~or~~

~~R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or~~

~~R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;~~

R^7 is selected from the group consisting of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^8 is selected from the group consisting of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{10} is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl,

optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$;

R^{11} and R^{12} each independently is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{13} is selected from the group consisting of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;

m is selected from the group consisting of 0, 1 and 2;

n is selected from the group consisting of 0, 1 and 2;

W is selected from the group consisting of ~~$S(O)_n$,~~ NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X ~~and Z each independently~~ is ~~selected from the group consisting of~~ O; ~~, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$;~~

Z is selected from the group consisting of NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is O;

and pharmaceutically acceptable salts thereof; wherein:

the substituents of an optionally substituted group comprise one or more substituents independently selected from among alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyester, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9, $NR^{10}R^{11}$, CF_2CF_3, CH_2CH_2F and CH_2CF_3.

2. (Previously presented) A compound according to claim 1, wherein R^1 is selected from the group consisting of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

3. (Previously presented) A compound according to claim 2, wherein R^1 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

4. (Previously presented) A compound according to claim 3, wherein R^1 is selected from the group consisting of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl.

5. (Previously presented) A compound according to claim 1, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

6. (Previously presented) A compound according to claim 5, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

7. (Previously presented) A compound according to claim 6, wherein R^2 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl.

8. (Original) A compound according to claim 7, wherein R^2 is CF_3.

9. (Currently amended) A compound according to claim 1, wherein

R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~; or~~

~~R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring~~.

Claim 10. (Cancelled)

11. (Previously presented) A compound according to claim 9, wherein R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

12. (Previously presented) A compound according to claim 1, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 -$

C_6 alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

13. (Previously presented) A compound according to claim 12, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl.

14. (Previously presented) A compound according to claim 13, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

15. (Previously presented) A compound according to claim 12, wherein R^6 is selected from the group consisting of optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroaryl.

16. (Previously presented) A compound according to claim 1, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_2 - C_6$ alkenyl.

17. (Previously presented) A compound according to claim 16, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

18. (Previously presented) A compound according to claim 17, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

19. (Original) A compound according to claim 18, wherein R^5 is hydrogen or CF_3.

20. (Previously presented) A compound according to claim 1, wherein R^7 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

21. (Previously presented) A compound according to claim 1, wherein R^8 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

22. (Original) A compound according to claim 21, wherein R^7 and R^8 are each hydrogen or optionally substituted $C_1 - C_2$ alkyl.

23. (Previously presented) A compound according to claim 1, wherein R^9 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

24. (Previously presented) A compound according to claim 23, wherein R^9 is selected from the group consisting of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

25. (Previously presented) A compound according to claim 1, wherein R^{10} is selected from the group consisting of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

26. (Previously presented) A compound according to claim 25, wherein R^{10} is selected from the group consisting of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$ and CO_2R^{12}.

27. (Previously presented) A compound according to claim 1, wherein R^4 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

28. (Previously presented) A compound according to claim 27, wherein R^4 is selected from the group consisting of hydrogen and optionally substituted $C_1 - C_2$ alkyl.

29. (Currently amended) A compound according to claim 1, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl,

optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~; or~~

~~R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring~~.

30. (Currently amended) A compound according to claim 29, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkenyl and optionally substituted aryl~~; or~~

~~R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring~~.

31. (Currently amended) A compound according to claim 30, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, allyl~~; or~~

~~R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring~~.

Claims 32 – 36 (Cancelled).

37. (Original) A compound according to claim 1, wherein m is 0 or 1.

38. (Original) A compound according to claim 37, wherein m is 1.

39. (Currently amended) A compound according to claim 1, wherein W is selected from the group consisting of NH, N{R^{13}} and N{C(Y)R^{11}}. ~~, N{C(Y)R^{11}} and N{SO_2R^{11}}.~~

40. (Original) A compound according to claim 39, wherein W is NH or N{R^{13}}.

Claims 41 and 42 (Cancelled).

Claims 43 and 44 (Cancelled).

Claim 45. (Cancelled).

46. (Original) A compound according to claim 45, wherein Z is NH or N{R^{11}}.

Claims 47 and 48 (Canceled).

49. (Currently amended) A compound according to claim 1, wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl;

R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$; ~~or~~

~~R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring;~~

R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl; and

R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~; or~~

~~R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring~~.

50. (Currently amended) A compound according to claim 49, wherein:

R^7 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl;

R^8 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl; and

R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$

haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~; or~~

~~R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring~~.

51. (Currently amended) A compound according to claim 50, wherein:

m is 0 or 1;

W is selected from the group consisting of NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}};

X is ~~selected from the group consisting of~~ O; ~~, S, NH and N{R^{11}}; and~~

Z is ~~selected from the group consisting of NH,~~ NH or N{R^{11}} ~~and O~~.

Claims 52 – 55 (Cancelled).

56. (Previously presented) A compound selected from the group consisting of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one ;

(3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R/S*)-4-Ethyl-2,3,4,7-tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta-[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(6a*R*)-6a,7,8,9 -Tetrahydro-4-(trifluoromethyl)-1*H*,6*H*-pyrrolo[1',2':4,5][1,4]-oxazino[2,3-*f*]quinolin-2-one;

2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-8-Chloro-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(3*R*) -3-Ethyl-3,4-dihydro-8-isopropoxy-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

a pharmaceutically acceptable salt thereof.

57. (Previously presented) A compound selected from the group consisting of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

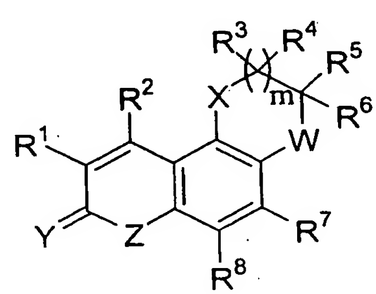
(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

a pharmaceutically acceptable salt thereof.

58. (Currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



(I)

wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^3 and R^4 each independently is selected from the group consisting of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; ~~or~~

~~R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or~~

~~R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;~~

R^5 and R^6 each independently are selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; ~~or~~

~~R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or~~

~~R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or~~

~~R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;~~

R^7 is selected from the group consisting of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^8 is selected from the group consisting of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{10} is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$;

R^{11} and R^{12} each independently is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{13} is selected from the group consisting of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;

m is selected from the group consisting of 0, 1 and 2;

n is selected from the group consisting of 0, 1 and 2;

W is selected from the group consisting of ~~$S(O)_n$,~~ NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X ~~and Z each independently~~ is ~~selected from the group consisting of~~ O; ~~, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$;~~

Z is selected from the group consisting of NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is O;

and pharmaceutically acceptable salts thereof; wherein:

the substituents of an optionally substituted group comprise one or more substituents independently selected from among alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyester, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9, $NR^{10}R^{11}$, CF_2CF_3, CH_2CH_2F and CH_2CF_3.

59. (Original) A pharmaceutical composition according to claim 58, wherein said composition is suitable for enteral, parenteral, suppository or topical administration.

60. (Previously presented) A pharmaceutical composition according to claim 58, wherein R^1 is selected from the group consisting of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

61. (Previously presented) A pharmaceutical composition comprising a compound according to claim 1, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

62. (Previously presented) A pharmaceutical composition according to claim 59, wherein:

R^1 is selected from the group consisting of hydrogen, F and optionally substituted C_1–C_4 alkyl; and

R^2 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl.

63. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$. ~~; or~~

~~R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.~~

64. (Previously presented) A pharmaceutical composition according to claim 58, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

65. (Previously presented) A pharmaceutical composition according to claim 64, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl.

66. (Previously presented) A pharmaceutical composition according to claim 58, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

67. (Previously presented) A pharmaceutical composition according to claim 66, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

68. (Previously presented) A pharmaceutical composition according to claim 58, wherein R^7 and R^8 each independently is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

69. (Previously presented) A pharmaceutical composition according to claim 58, wherein:

R^9 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, and optionally substituted $C_1 - C_6$ heteroalkyl; and

R^{10} is selected from the group consisting of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

70. (Previously presented) A pharmaceutical composition according to claim 58, wherein R^4 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

71. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~; or~~

~~R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring~~.

72. (Currently amended) A pharmaceutical composition according to claim 71, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, and allyl~~; or~~

~~R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring~~.

Claims 73 and 74 (Canceled).

75. (Original) A pharmaceutical composition according to claim 58, wherein m is 0 or 1.

76. (Currently amended) A pharmaceutical composition according to claim 58, wherein:

W is selected from the group consisting of NH, ~~$N\{R^{13}\}$,~~ $N\{R^{13}\}$ and $N\{C(Y)R^{11}\}$; and

~~$N\{SO_2R^{11}\}$; and~~

X is ~~selected from the group consisting of~~ O. ~~, NH and $N\{R^{11}\}$.~~

77. (Currently amended) A pharmaceutical composition according to claim 58, wherein Z is ~~selected from the group consisting of NH, NH or~~ $N\{R^{11}\}$. ~~and O.~~

Claims 78 – 107 (Cancelled).

108. (New) The compound of claim 1, wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and o $C_2 - C_8$ alkenyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl;

R^3 and R^4 each independently is selected from the group consisting of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl;

R^5 and R^6 each independently is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_3 - C_8$ cycloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl;

R^7 is selected from the group consisting of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^8 is selected from the group consisting of hydrogen, F, Cl, Br, I, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^9 is selected from the group consisting of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl;

R^{10} is selected from the group consisting of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl, arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$;

R^{11} and R^{12} each independently is selected from the group consisting of hydrogen, $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, aryl, heteroaryl and arylalkyl;

R^{13} is selected from the group consisting of $C_1 - C_8$ alkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ heteroalkyl, $C_2 - C_8$ alkenyl, $C_2 - C_8$ alkynyl, $C_3 - C_8$ cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl;

m is selected from the group consisting of 0, 1 and 2;

n is selected from the group consisting of 0, 1 and 2;

W is selected from the group consisting of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X is O;

Z is selected from the group consisting of NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is O;

and pharmaceutically acceptable salts thereof

REMARKS

A check for $120 for the fee for a one-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is needed, this paper is to be considered such Petition. Supporting art accompanies this response.

Claims 1-9, 11-31, 37-40, 46, 49-51, 56-72, 75-77 and 108 are pending. Claims 10, 41, 42 and 45 are cancelled herein without prejudice or disclaimer. Applicant reserves the right to file a continuation application directed to cancelled subject matter. Claims 1, 9, 29-31, 49-51, 58, 63, 71, 72, 76 and 77 are amended herein to more distinctly claim the subject matter. Claims 1 and 58 are amended to define the substituents of the optionally substituted groups. Basis for the amendment is found throughout the specification (*e.g.*, see page 11, line 26 through page 12, line 9). Claims 1 and 58 also are amended to separate the substituents for variables X and Z. Claims 1, 9, 29-31, 49, 50, 58, 63, 71 and 72 are amended to cancel subject matter directed to substituents that when taken together form a carbocyclic or heterocyclic ring. Applicant reserves the right to file a continuation application directed to cancelled subject matter. Claims 51 and 76 are amended to more distinctly claim the substituents for X and Z. Basis for new claim 108 is found throughout the specification (for example, see pages 3-7 and original claim 1).. No new matter is added.

THE REJECTION OF CLAIMS 1-31, 37-42, 45, 46, 49-51, 58-72 AND 75-77 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH – Scope of Enablement

Claims 1-31, 37-42, 45, 46, 49-51, 58-72 and 75-77 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter not described in the specification in such a way as to enable one of skill in the art to make and/or use the claimed subject matter. The Examiner states that the compound and pharmaceutical composition claims are only enabled in part because the instant claims include terms that allegedly are incompletely defined. The Examiner also alleges that it would require undue experimentation to practice the full scope of the claims. The Examiner alleges that "the scope is excessive in view of the disclosed exemplifications." Applicant respectfully traverses the rejection.

RELEVANT LAW

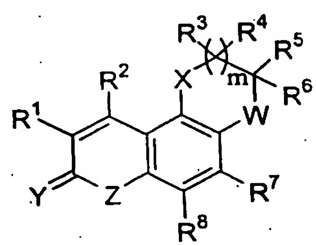
The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d

1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). Indeed, "not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted." *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332. Showing every combination of substituents is unnecessary.

A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *See, Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

THE CLAIMS

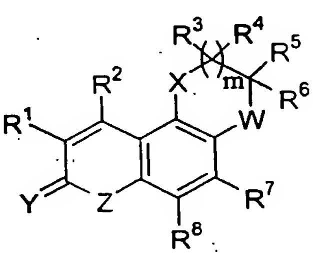
Claim 1 is directed to a compound having the formula:



(I)

where the substituents are as recited in the claims. Claims 2-9, 11-31, 37-40, 46 and 49-51 ultimately depend from claim 1 and are directed to various embodiments thereof.

Claim 58 is directed to a pharmaceutical composition that includes a pharmaceutically acceptable carrier and a compound of formula:



(I)

where the substituents are as recited in the claims. Claims 59-72, 75 and 76 ultimately depend from claim 58 and are directed to various embodiments thereof.

ANALYSIS

Applicant respectfully submits that the Examiner rejects claims 1-31, 37-42, 45, 46, 49-51, 58-72 and 75-77 under 35 U.S.C. § 112, first paragraph on page 2 and on page 3 of the Office Action. Both rejections state that the claims are rejected because it is alleged that practicing the full scope of the claims requires undue experimentation. Applicant respectfully requests that the Examiner clarify the difference between the rejection on page 2 and the rejection on page 3 of the Office Action so that Applicant can address the rejections with particularity. In order to be fully responsive, Applicant provides the following traverse.

The *In re Wands* factors

Applying the *In re Wands* factors to the instant facts reveals that the amount of experimentation is not undue. The analysis and arguments set forth in the previous responses of record are incorporated by reference herein.

a. The scope of the claims.

The pending claims recite compounds of Formula I and compositions thereof. The Examiner alleges that:

> The repeated use of the term "may be optionally substituted" without specifying the substituents implied thereby renders the breadth of the claim excessive because said term implies that the unnamed substituents is/are open to all possible alternatives.

First, the pending claims do not include the recitation "may be optionally substituted." The pending claims include the recitation "optionally substituted." Further, as discussed above, claims must be read in view of the specification. See *e.g.*, MPEP § 2106 ("An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim."); MPEP § 608.01(o) ("The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification"); MPEP § 2173.05 ("When the specification states the meaning that a term in the claims is intended to have, the claim is examined using that meaning in order to achieve a complete exploration of the applicant's invention and its relation to the prior art."). The term "optionally substituted" is expressly defined in the specification. Thus, the recitation "optionally substituted" does not imply "that the unnamed substituents is/are open to all possible alternatives" as alleged by the Examiner. Thus, reciting that definition in the claims is not necessary. Without a acquiescing to the Examiner's allegation and solely to expedite issuance of the application, independent claims 1

and 58 are amended herein to recite the substituents encompassed by the recitation "optionally substituted" in the claims.

b. Nature of the Invention

The specification provides a general description of non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists (*i.e.*, partial activators and/or tissue-specific activators) and antagonists for androgen receptors (AR). The claimed subject matter is directed to androgen receptor modulator compounds and pharmaceutical compositions containing such compounds.

The Examiner states that the nature of the invention "includes a method of testing, a method of purification and a vast number of medicinal treatment[s] wherein compounds of instant claim 1 are administered to a host in need of such treatment." Applicant respectfully submits that the pending claims are directed to compounds as recited in the claims and to pharmaceutical compositions thereof. There currently are no method claims pending.

c. State of the Prior Art

Applicant respectfully submits that, at the time of the priority application, the mechanism of action of the intracellular receptors and the effects of small molecule agonists, antagonist or partial agonists on IR-mediated transcription modulation was well known to the skilled artisan (for example, see Rosen *et al.* (*J. Med. Chem.*, 1995, vol. 38, No. 25, pp 4855-4874, a copy of which is provided herein). Androgen receptor agonist compounds and their use as therapeutic agents also was known to those skilled in the medical arts. For example, Rosen *et al.* provides an overview of diseases and conditions that share mediation by androgen receptors as an underlying etiology. For example, Rosen *et al.* recites on page 4862:

> "Androgens are synthesized in the testes, adrenal cortex, and ovaries. The net effect of endogenous androgens reflects the combined actions of the secreted hormone, testosterone; its 5α-reduced metabolite, dihydrotestosterone; and its estrogenic derivative, estradiol. Androgens serve different functions at different stages of male development and have clear therapeutic uses in the treatment of hypogonadism, growth retardation, breast carcinoma, and osteoporosis. The actions of androgens are mediated through AR."

Applicant also submits that at the time of the priority application, androgen receptor agonist compounds were either in clinical trials or were available to the public for the treatment of hypogonadism, metastatic breast cancer, anemias, as anabolic agents and for the treatment of other diseases or conditions. For example, Testoderm®, a testosterone transdermal patch, was approved in the U.S. in 1993 for hormone replacement therapy in hypogonadal men. Androderm®, also a transdermal testosterone patch, was approved in the

U.S. in 1995 for the treatment of hypogonadism. Testred®, which contains the AR agonist methyltestosterone, was approved in the U.S. in 1973 for hormone replacement therapy in hypogonadal men as well as for the treatment of metastatic breast cancer in women. Anadrol®-50, which contains the AR agonist oxymetholone, was approved in the U.S. in 1972 and is used in the treatment of anemias caused by deficient red cell production. It also is well known that testosterone, the native androgen and AR agonist, is an anabolic agent. Therefore, it was well known in the prior art at the time of filing the original application that androgen receptor agonist compounds and compositions that include AR agonist compounds are useful in male hormone replacement therapy, in stimulation of hematopoiesis, as anabolic agents, and in the treatment of wasting diseases, hypogonadism and breast cancer.

Applicant also respectfully submits that, at the time of filing the priority application, the use of androgen receptor antagonists as therapeutic agents was known to those skilled in the medical arts. For example, Singh *et al.*, teaches that androgen receptor antagonists are useful for treating prostate cancer, acne, seborrhea, hirsuitism and androgenic alopecia (Singh *et al.*, Current Medicianl Chemistry 7: 211-247 (2000)). Rosen *et al.* (*J. Med. Chem.*, 1995, vol. 38, No. 25, pp 4855-4874) also provides an overview of diseases and conditions that share an etiology of being mediated by androgen receptor antagonists. For example, Rosen *et al.* recites on page 4862:

> "Compounds that block the action or synthesis of androgens have proven useful in treatment of diseases such as prostate cancer, prostatic hypertrophy, hirsutism, male pattern baldness, and acne. Among the most potent orally active anti-androgens is cyproterone acetate. This compound possesses progestational activity and suppresses the secretion of gonadotrphins, both of which are unwanted side effects. Other anti-androgens include flutamide, a prodrug for the active metabolite, 2-hydroxyflutamide, casodex, and an analogue of nilutamide."

Applicant also submits that at the time of filing the instant application, several androgen receptor antagonist compounds were either in clinical trials or were available to the public for the treatment of the diseases or conditions listed above. For example, Eulexin®, which contains the androgen receptor antagonist flutamide, was approved in the U.S. in 1989 for the treatment of prostate cancer. Casodex® (bicalutamide), an androgen receptor antagonist, was approved in 1995 for the treatment of prostate cancer. The AR antagonist cyproterone acetate was approved for use in Europe as early as 1978 for the treatment of female acne and hirsutism (Gruber *et al.*, Arch Dermatol 134: 459-463 (1998), Venturoli *et al*, J Clin Endocrinology & Metabolism 84(4): 1304-1310 (1999)).

In addition, a number of methods and assays for identifying agonists, partial agonists or antagonists of the steroid receptors was known at the time of filing the original application. For example, Berger *et al.* teaches a co-transfection assay (Berger *et.al.*, J. Steroid Biochem. Molec. Biol. **41**: 773 (1992)). Berger *et al.* teaches that activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology.

Thus, at the time of filing of the instant application, a broad body of knowledge had amassed in the areas of pharmaceutical sciences, medicine, and biochemistry directed to compounds that agonize or antagonize the steroid receptors, including androgen receptors, and to the use of compounds that agonize or antagonize the steroid receptors, such as androgen receptors, for treatment of diseases and conditions.

d. Level of Skill in the Art

As the Examiner noted, the skill in the art of chemical synthesis is high. That skill, together with the instant specification, including cited and incorporated references, allow the skilled artisan to make any and all of the claimed compounds. The Examiner states that "the level of skill in the medicinal arts is moderate because it is unclear which if any of the compounds disclosed herein are active against one or more specific disease conditions." Applicants respectfully disagree. The level of skill in the medical arts is independent of the issues. The skill of the medical practitioner does not vary.

Applicant respectfully submits that the level of skill in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

With respect to the rejection, it is respectfully submitted that no evidence is provided to support the Examiner's position that "the level of skill in the medicinal arts is moderate because it is unclear which if any of the compounds disclosed herein are active against one or more specific disease conditions." The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well- known" in the art. *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The facts of which the Examiner is taking notice are conclusory and are not capable of instant and unquestionable demonstration as being "well-known" in the art. MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. *In re Malcolm*, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

If this position is maintained, the Examiner must provide a reference supporting this position.

e. Predictability of the Art

The Examiner alleges that the level of predictability in the art is indeterminate because it allegedly is not clear which compounds are active as androgen receptor agonists or antagonists. Applicant respectfully disagrees.

The instant application provides detailed teachings of *in vitro* and *in vivo* assays that allow one of skill in the art to test the compounds as instantly claimed for androgen receptor activity. The instant application, for example pages 110-114, provides a highly detailed teaching of *in vitro* assays, such as the "cis-trans" or "co-transfection" assay. Table 1 on page 115 of the specification provides *in vitro* binding data of exemplary compounds disclosed in the instant application that exhibit androgen receptor agonist activity, partial agonist activity, or antagonist activity. These assays are known in the art (see Evans *et al.*, Science 240: 889-95 (1988) and correlate well with *in vivo* activity and can function as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology (Berger *et al.*, J. Steroid Biochem. Molec. Biol. 41: 773 (1992)). The data indicates that all of the exemplary compounds possess androgen receptor agonist, partial agonist or antagonist activity.

The compounds of the instant application are further characterized for their specificity for the androgen receptor by examining the *in vitro* binding activity with other members of the steroid receptors. Table 2 on page 116 provides binding data for exemplary compounds disclosed in the instant application with the androgen, progesterone, estrogen, glucocorticoid and mineralcorticoid receptors. As noted above, the androgen receptor agonist activity or antagonist activity shown in the *in vitro* assays correlates very well with *in vivo* activity. Once the androgen receptor activity of the compounds have been established, the application of those compounds to the treatment of any diseases responsive to androgen receptor agonists or antagonists, as discussed above, is well within the routine skills of those skilled in the art through reference to the present specification as well as the general and specialized knowledge of those working in this recognized field. Further, formulating such compounds into a

pharmaceutical composition and administration of such compositions to a subject is well known in the medical arts.

f. The amount of direction or guidance presented and the presence of working examples

The Examiner admits that the specification discloses 150 exemplary compounds that are precursors, intermediates or final products of the claimed compounds. The specification also teaches seven generic synthesis schemes (for example, see page 33, 35, 37, 38, 39, 41 and 42). The application names over 150 exemplary AR modulator compounds (for example, see page 29 through 32 and claims 56 and 57). The specification also provides over 50 working examples and two screening assays. It is respectfully submitted that the direction provided by the specification is sufficient to allow one of skill in the art to synthesize, test and administer any and all compounds of the claimed subject matter. Modification of the reaction conditions or choice of starting materials is routine and within the scope of the teachings in the application and knowledge of one of skill in the art.

For example, Scheme I outlines the synthesis of 5-hydroxy-6-bromo-quinoline compounds **6** starting from a phenylenediamine derivative, for example, 5-chloro-1,3-phenylenediamine. Other phenylenediamine derivatives also can be used in the synthetic sequence outlined in Scheme I. For example, use of 5-chloro-1,4-phenylenediamine as the starting material in Scheme I results in the synthesis of 6-hydroxy-5-bromo-quinoline compounds.

Schemes III and V outline the synthesis of 7-nitro-1,4-benzoxazine compounds, which begin with the chemo- and regioselective N-alkylation of an amino alcohol onto a 3,4-dihalonitrobenzene, such as, for example, 3,4-difluoronitrobenzene. One of skill in the art would recognize that selective protection of the nitrogen atom of the aminoalcohol **13**, with, for example, di-tert-butyl dicarbonate, prior to reaction with 3,4-difluoronitrobenzene would result in the reaction of the alcohol moiety of the aminoalcohol at the 4-position of 3,4-difluoronitrobenzene. Removal of the protecting group on the nitrogen, with, for example, acid, followed by treatment with base would provide 6-nitro-1,4-benzoxazine compounds, which are regioisomers of structures **15** and **24**.

Scheme VI outlines a racemic route to 7-nitro-1,4-benzoxazine compounds **24** that begins with the *N*-alkylation of a 2-amino-5-nitrophenol by treatment with an aldehyde, its corresponding hydrate or hemiacetal, in the presence of a reducing agent, for example, sodium cyanoborohydride. However, use of a 2-amino-4-nitrophenol derivative as the starting material, instead of 2-amino-5-nitrophenol as depicted in Scheme VI, would provide 6-nitro-

1,4-benzoxazine compounds. 6-Nitro-1,4-benzoxazine compounds are regioisomers of compounds of structure 24. One of skill in the art can readily follow these schemes or known variations of such schemes with any of a vast number of commonly available starting materials to arrive at the claimed subject matter. The art of chemical synthesis is predictable and is dictated by recognized chemical reactions and constraints. There is nothing of record to suggest that production or use of any of the claimed compounds or compositions would require development of new procedures or excessive experimentation. Organic synthesis methods have been used for decades. Hence, any experimentation would be routine to the skilled artisan. Therefore, in view of the teachings of the specification, in combination with what was known at the time the priority application was filed, Applicant respectfully submits that the claimed compounds can be prepared predictably using the methods disclosed in the specification or that are known to those skilled in this art.

Similarly, one of skill in the art can assess the activity of any of the claimed compounds using the binding assay or the co-transfection assay, both of which are disclosed in the specification, though one of skill in the art can assess compounds using other known assays. Various screening assays for assessing the ability of a compound or composition to modulate the transcriptional ability of intracellular receptors are known to those of skill in the art, such as those described in U.S. Pat. Nos. 4,981,784, 5,071,773, 5,298,429, and 5,506,102 and in WO89/05355, WO91/06677, WO92/05447, WO93/11235, WO93/23431, WO94/23068, WO95/18380 and CA 2,034,220. Further, formulating such compounds into a pharmaceutical composition and administration of such compositions to a subject is well know in the medical arts. Thus, preparation and administration of pharmaceutical compounds also is predictable. Finally, administration of compounds is routine to one of skill in the medical arts. Thus, it is respectfully submitted that the direction provided by the specification is sufficient to allow one of skill in the art to synthesize, test and administer any and all compounds of the claimed subject matter. Therefore, Applicant respectfully submits that one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation.

g. The amount of experimentation required

There is nothing of record to suggest that production or use of any of the claimed compounds or compositions would require development of new procedures or excessive experimentation. Organic synthesis methods have been used for decades. As discussed above, bioassays for evaluating whether compounds are functional ligands for receptor

proteins were known in the art since at least 1991. Such assays are routine in this art and do not require excessive experimentation. Applicant notes that "a considerable amount of experimentation is permissible, if it is merely routine . . ." *In re Wands* 858 F.3d 731, 737 (Fed Cir. 1988).

CONCLUSION

In light of the scope of the claims, the nature of the claimed subject matter, the state of the prior art, the high level of skill of those in this art, the predictability of the art, the amount of direction and guidance presented in the specification, the presence of over 50 working examples, the low amount of experimentation required and the fact that any required experimentation is routine, Applicant respectfully submits that it would not require undue experimentation for a person skilled in the art to make and use the claimed compounds and compositions. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

1. "Disclosed Exemplifications"

The Examiner alleges that the scope is excessive in view of the "disclosed exemplifications." Applicant respectfully disagrees. The specification discloses androgen receptor modulator compounds, pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating processes mediated by steroid receptors. The application discloses methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis. The specification describes seven generic synthesis schemes (for example, see page 33, 35, 37, 38, 39, 41 and 42). One of skill in the art can readily follow these schemes or known variations of such schemes with any of a vast number of commonly available starting materials to arrive at the claimed subject matter. The application names over 150 exemplary AR modulator compounds (for example, see page 29 through 32 and claims 56 and 57. The specification also provides over 50 working examples. The application teaches *in vitro* assays, such as the "cis-trans" or "co-transfection" assay, for characterizing exemplary AR modulator compounds. The specification provides *in vitro* binding data of exemplary compounds disclosed in the instant application that exhibit androgen receptor agonist activity, partial agonist activity, or antagonist activity. The compounds of the instant application are further characterized for their specificity for the androgen receptor by examining the *in vitro* binding activity with other members of the

steroid receptors. Hence the specification provides a variety of examples of compounds that fall within the scope of the claims evidencing that the claimed compounds function as claimed. The requirements of 35 U.S.C. §112, first paragraph, do not require a specific example of everything within the scope of the claims. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973) :

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

Hence there is no requirement for the applicant to exemplify or even provide an example of everything within the scope of the claims. The Patent Office cannot "limit all claims to the specific examples, notwithstanding the disclosure of a broader invention." A patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935). Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

2. **"Defined by the Prior Art"**

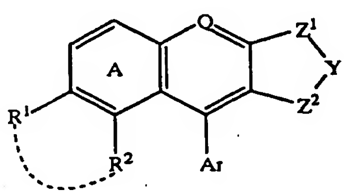
In the present Action, the Examiner alleges that "the state of the prior art is defined by the prior art presently cited by the Applicant and by Examiner and particularly by PTO-892 references F and G wherein anticipatory compounds and compositions have been disclosed." Applicant respectfully disagrees. The prior art is replete with references that show that the skilled artisan can use known organic synthesis schemes and reactions to produce various bicyclic, tricyclic and polycyclic organic compounds, including, for example, quinolines, quinolinones, coumarins, benzoxyzins, oxazolidines, azasteroids, progesterones, azachlor-madinones, anthrasteroids, flutamides and phthalimides, and that the art of record teaches bioassays for evaluating whether compounds are functional ligands for receptor proteins and correlates the activity of ligands in such assays to *in vivo* activity (*e.g.*, see Evans *et al.* (US Pat. Nos. 4,981,784 and 5,071,773 and Science 240:889-95 (1988)).

Applicant disagrees that "the state of the prior art is defined by the prior art presently cited by applicant and by examiner." Applicant is not aware of such a definition and respectfully requests that the Examiner cite authority.

3. Alleged Anticipatory Prior Art

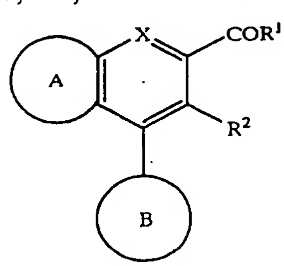
In the present Action, the Examiner alleges that certain references are anticipatory prior art (Action at page 4, which states that PTO-892 references F and G disclose anticipatory compounds and compositions). Reference F is US 6,030,967 (2/29/00) to Mauri *et al.* and Reference G is US 6,340,704 (1/22/02) to Mauri *et al.* Applicant respectfully submits that the Examiner has not rejected any of the claims under 35 U.S.C. § 102(b) as anticipated by either US Pat. Nos. 6,030,967 or 6,340,704. Applicant respectfully submits that neither US Pat. No. 6,030,967 nor US Pat. No. 6,340,704 discloses compounds as instantly claimed nor compositions thereof.

For example, US Pat. No. 6,030,967 discloses compounds having the formula:



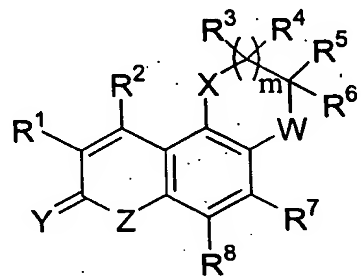
where Q is an optionally substituted carbon atom or $N(O)_p$ wherein p is 0 or 1; Y is an optionally substituted methylene group, $S(O)_q$ wherein q is an integer of 0 to 2, or an optionally substituted imino group; Z^1 is a C_{1-3} alkylene group which can have an oxo group or a thioxo group and can contain etherified oxygen or sulfur within the carbon chain; Z^2 is an optionally substituted C_{1-3} alkylene group; Ar is an optionally substituted carbocyclic group or an optionally substituted heterocyclic group; one of R^1 and R^2 is a hydrogen atom, a halogen atom, a hydroxyl group, an optionally substituted lower alkyl group, or an optionally substituted lower alkoxy group; the other is a halogen atom, a hydroxyl group, an optionally substituted lower alkyl group, or an optionally substituted lower alkoxy group; or R.sup.^{1} and R.sup.^{2} taken together with adjacent –c=c– form a ring; and ring *A* is a benzene ring which may be substituted in addition to R^1 and R^2 ; or a salt thereof.

US Pat. No. 6,340,704 discloses compounds having the formula:



where R^1 is an amino group that may be substituted, R^2 is a hydrogen atom or a lower alkyl group that may be substituted; X is a methane group that may be substituted or $N(O)_m$ (m is 0 or 1); ring *A* is a homo- or hetero-cycle that is substituted by a halogen atom, lower alkyl, lower alkoxy or lower alkylenedioxy group, and ring *B* is a homo- or hetero-cycle that may be substituted.

Neither US Pat. No. 6,030,967 nor US Pat. No. 6,340,704 discloses compounds or compositions as instantly claimed, such as those that have the structure set forth as formula I



I

and defined in the instant claims. Applicant also respectfully submits that the Office Action is internally inconsistent. At Paragraph C on Page 4 of the Action the Examiner alleges that PTO-892 References F and G disclose anticipatory compounds and compositions, while in Paragraph D on Page 4 of the Action, the Examiner states that these references disclose "many compounds very closely analogous to the instant claimed compounds." Further, on page 6 of the Action, the Examiner states that "claims 1-31, 37-42, 45, 46, 49-51, 58-72 and 75-77 would be allowable if rewritten or amended to overcome the rejection under 35 U.S.C. 112" (see last sentence on page 6). Thus, it appears that the Examiner is mistaken when he states on page 4 of the Action that US Pat. No. 6,030,967 and US Pat. No. 6,340,704 disclose anticipatory compounds and compositions. In order to clarify the record of the instant prosecution history, Applicant respectfully requests that the Examiner withdraw the statement that US Pat. No. 6,030,967 and US Pat. No. 6,340,704 disclose anticipatory compounds and compositions.

4. The instant claims include terms that allegedly are incompletely defined

The Examiner alleges that the compounds and pharmaceutical composition claims are enabled only in part because the instant claims include terms that allegedly are incompletely defined. The prior Office Action raised this issue under 35 U.S.C. § 112, second paragraph, and it has not been maintained in the instant Action. Thus, it appears that the rejection under 35 U.S.C. § 112, second paragraph has been withdrawn. Notwithstanding this, in order to be fully responsive, Applicant respectfully traverses the rejection.

a. aryl

The Examiner alleges that the term "aryl" is incompletely defined because "said terms typically i) lack any upper bounds as to size." Applicant respectfully disagrees.

It is respectfully submitted that the specification specifically defines the term "aryl." For example, page 9, line 26 through page 10, line 5, recites:

> The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from six to about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

This definition includes upper bounds as to size. Applicant respectfully submits that claims must be read in view of the specification. See, *e.g.*, MPEP § 2106 ("An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim."); MPEP § 2173.05 ("When the specification states the meaning that a term in the claims is intended to have, the claim is examined using that meaning in order to achieve a complete exploration of the applicant's invention and its relation to the prior art."). The term "aryl" is expressly defined in the specification, and the definition recites specifics that the Examiner alleges to be missing ("bounds as to size"). Thus, the term "aryl" is not incompletely defined. Therefore, reciting the definition for "aryl" in the claims is not necessary.

b. arylalkyl

The Examiner alleges that the term "arylalkyl" is incompletely defined because "said terms typically i) lack any upper bounds as to size." Applicant respectfully disagrees. The term "arylalkyl" is defined in the specification. For example, see page 11, lines 9-11, which recites:

> The term "arylalkyl," alone or in combination, refers to an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The term "arylalkyl" is expressly defined in the specification, and references the terms "alkyl" and "aryl." As discussed above, the specification defines the recitation "aryl" (*e.g.*, see page 9, line 26 through page 10, line 5). In addition, the specification defines the recitation "alkyl" (*e.g.*, see page 8, lines 13-18):

> an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, *tert*-amyl, pentyl, hexyl, heptyl, octyl and the like.

The definitions provided in the specification for the terms "alkyl" and "aryl" recites the "upper bounds as to size" that the Examiner alleges to be missing. Thus, one of skill in the art would be apprised of the metes and bounds of the term "arylalkyl" when read in light of the specification. Therefore, reciting the definition for "arylalkyl" in the claims is not necessary.

c. heteroaryl

The Examiner alleges that the term "heteroaryl" is incompletely defined because:

> said terms typically
> i) lack any upper bounds as to size,
> and when heteroatoms are suggests said terms
> ii) fail to define which hetero atoms are to be selected from
> iii) the number of said heteroatoms, or
> iv) the location(s) or the ring system(s) containing said heteroatom(s) and
> v) because a proper definition of "optionally substituted" is not present in any independent claim.

Applicant respectfully submits that the specification defines the recitation "heteroaryl" (*e.g.*, see page 10, lines 6-19):

> optionally substituted aromatic ring systems containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidoyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

The definition set forth in the specification for the term "heteroaryl" recites the "upper bounds as to size" that the Examiner alleges to be missing. The definition also states that the rings include one or more heteroatoms, such as oxygen, nitrogen and sulfur. Thus, Applicant respectfully submits that one of skill in the art, in light of what is known in the art and the teachings of the

specification, would understand what is meant by the recitation "heteroaryl" and would be able to determine the metes and bounds of the claims. Thus, reciting the definition for "heteroaryl" in the claims is not necessary.

d. "optionally substituted"

The term "optionally substituted" is defined in the specification at page 11, line 26 to page 12, line 9, which states:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$).

Thus, the recitation "optionally substituted" does not imply "that the unnamed substituents is/are open to all possible alternatives" as alleged by the Examiner. As discussed above, claims must be read in view of the specification. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. The term "optionally substituted" is expressly defined in the specification. Thus, reciting that definition in the claims is not necessary.

Furthermore, the USPTO recognizes the use of this term in patent claims. A search of the USPTO database for the time period 1976 to present for patents with the recitation "optionally substituted" in the claims yielded 22,359 patents. While applicant realizes that the prosecution history of one patent is not relevant to another, the widespread use of the recitation "optionally substituted" in claims evidences that one of skill in the art understands the meaning of this term.

Notwithstanding the above, without acquiescing to the Examiner's allegation and solely to expedite issuance of the application, independent claims 1 and 58 are amended herein to recite the substituents encompassed by the recitation "optionally substituted" in the claims.

5. Spiro structures

The Examiner alleges that no heterocyclic or homocyclic spiro examples are included in any of the synthetic schemes or any of the specific compounds in the application.

Without a acquiescing to the Examiner's allegation and solely to expedite prosecution, claim 10 is cancelled herein without prejudice or disclaimer and claims 1, 9, 29-31, 49, 50, 58, 63, 71 and 72 are amended to delete recitations where two particular substituents together form a carbocyclic or heterocyclic ring. Thus, the rejection is moot. Applicant expressly reserves the right to pursue the cancelled subject matter in a continuing application.

6. The definitions of variables X and Z

The Examiner suggests that the definitions of variables "X" and "Z" should be separated. Without a acquiescing to the Examiner's allegation and solely to expedite prosecution and advance the application to issuance, claims 1 and 58 are amended herein to define the variables "X" and "Z" separately.

REJECTION OF CLAIMS 1-7, 9, 11-18, 20-25, 27-30, 49, 58, 60-62, 64-71, 73 AND 74 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 9, 11-18, 20-25, 27-30, 49, 58, 60-62, 64-71, 73 and 74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that the recitation "optionally substituted" fails "to specify the substituents implied thereby." The Examiner also alleges that the definition for "optionally substituted" in the specification is "inadequate because the definition fails to meet the requirements of the statute for a variety of reasons noted in examiner's response following a previous rejection."

Applicant respectfully traverses the bases for the rejection in turn below.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984). Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), *cert. dismissed*, 106 S.Ct. 340 (1985).

ANALYSIS

<u>"Optionally substituted"</u>

As discussed above, the term "optionally substituted" is defined in the specification (*e.g.*, see page 11, line 26 to page 12, line 9). Claims must be read in view of the specification. Where an explicit definition is provided by the applicant for a term, that definition will control

interpretation of the term as it is used in the claim (see *e.g.*, MPEP § 2106). The term "optionally substituted" is defined in the specification and thus that definition will control interpretation of the claim. Thus, reciting the definition in the claims is not necessary.

Notwithstanding this, without a acquiescing to the Examiner's allegation and solely to expedite issuance of the application, independent claims 1 and 58 are amended herein to recite the substituents encompassed by the recitation "optionally substituted" in the claims.

Alleged "Inadequate" Definition

The Examiner does not distinctly recite the alleged deficiencies in the definition for the recitation "optionally substituted" provided in the specification. Applicant respectfully requests that the Examiner restate the rejection with particularity to afford the applicant an opportunity to properly respond. In order to be fully responsive, Applicant provides the following traverse.

The Examiner objects to the definition of "optionally substituted" recited in the specification because it includes the terms "aryl," "arylalkyl" and "heteroaryl" because:

said terms typically
i) lack any upper bounds as to size,
and when heteroatoms are suggests said terms
ii) fail to define which hetero atoms are to be selected from
iii) the number of said heteroatoms, or
iv) the location(s) or the ring system(s) containing said heteroatom(s) and
v) because a proper definition of "optionally substituted" is not present in any independent claim.

a. aryl

The specification specifically defines the term "aryl." For example, page 9, line 26 through page 10, line 5, recites:

> The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from six to about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

This definition includes upper bounds as to size. Thus, the term "aryl" is not incompletely defined.

b. arylalkyl

The term "arylalkyl" is defined in the specification. For example, see page 11, lines 9-11, which recites:

> The term "arylalkyl," alone or in combination, refers to an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The terms "alkyl" and "aryl" are defined in the specification. As discussed above, the definition for the term "aryl" recites the "upper bounds as to size" that the Examiner alleges to be missing. Thus, the term "arylalkyl" is not incompletely defined.

c. heteroaryl

The specification defines the recitation "heteroaryl" (*e.g.*, see page 10, lines 6-19):

> optionally substituted aromatic ring systems containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyheteroaromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (*e.g.*, a six membered ring with two nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidoyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

The definition set forth in the specification for the term "heteroaryl" recites the "upper bounds as to size" that the Examiner alleges to be missing. The definition also states that the rings include one or more heteroatoms, such as oxygen, nitrogen and sulfur. Thus, Applicant respectfully submits that one of skill in the art, in light of what is known in the art and the teachings of the specification, would understand what is meant by the recitation "heteroaryl" and would be able to determine the metes and bounds of the claims. Thus, the term "heteroaryl" is not incompletely defined.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

The Definition of Variable R^{18}

In the rejection under 35 U.S.C. 112, second paragraph, the Examiner alleges the recitation "may be optionally substituted" has been replaced with the recitation "optionally substituted" in the claims except in the case of variable R^{18} in claims 1 and 58. Without

addressing the propriety of the rejection, Applicant respectfully submits that neither claim 1 nor claim 58 recites a variable R^{18}. Thus, because claims 1 and 58 do not recite a variable R^{18}, this rejection is moot.

* * *

In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

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Attorney's Docket No.: 18202-018001 / 1082

RESPONSE UNDER 37 CFR §1.116
– EXPEDITED PROCEDURE –
EXAMINING GROUP 1600

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHOD**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.

MAIL STOP AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUPPORTING DOCUMENTS

1. Rosen *et al.*, J. Med. Chem. 38(25): 4855-4874 (1995).
2. TESTODERM (Brand name drug), NDA 019762, Approval History, US Food and Drug Administration; Approval – October 12, 1993.
3. ANDRODERM (Brand name drug), NDA 020489, Approval History, US Food and Drug Administration; Approval – September 29, 1995.
4. ANADROL-50 (Brand name drug), NDA 016848, Approval History, US Food and Drug Administration; Approval – January 18, 1972.
5. TESTRED (Brand name drug), ANDA 083976, Approval History, US Food and Drug Administration; Approval – December 3, 1973.
6. EULEXIN (Brand name drug), NDA 018554, Approval History, US Food and Drug Administration; Approval – January 27, 1989.
7. CASODEX (Brand name drug), NDA 020498, Approval History, US Food and Drug Administration; Approval – October 4, 1995.
8. Gruber *et al.*, Arch Dermatol 134: 459-463 (1998).
9. Venturoli *et al*, J Clin Endocrinology & Metabolism 84(4): 1304-1310 (1999).
10. Berger *et al.*, J. Steroid Biochem. Molec. Biol. 41: 773-738 (1992).

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Confirmation No.: 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT & RESPONSE

Dear Sir:

Responsive to the Office Action, mailed May 3, 2005, entry of the following amendments and consideration of the following remarks are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 22 of this paper.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
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I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

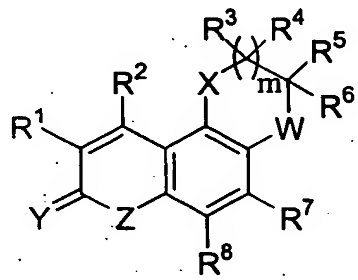
Frank J. Miskiel

Amendments to the Claims:

Claims 1-30, 37-42, 45, 46, 49-51, 56-72 and 75-77 are pending. Claims 32-36, 43, 44, 47, 48, 52-55, 74, 74 and 80-107 are cancelled without prejudice or disclaimer. Claims 1-7, 9, 11-18, 20, 21, 23-31, 39, 41, 45, 49-51, 56-58, 60-72 and 76 are amended. This listing of claims will replace all prior versions, and listings, of claims in the application:

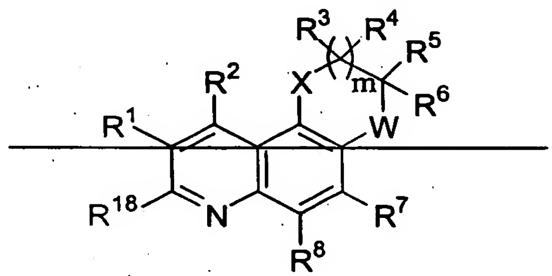
Listing of Claims:

1. (Currently amended) A compound having the formula:



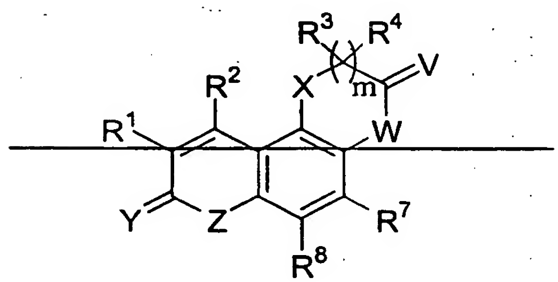
(I)

~~OR~~



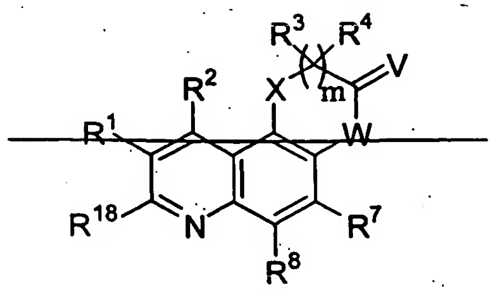
~~(II)~~

~~OR~~



~~(III)~~

~~OR~~



~~(IV)~~

wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^3 and R^4 each independently is selected from the group consisting of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group <u>consisting</u> of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^8 is selected from the group <u>consisting</u> of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^9 is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{10} is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$;

R^{11} and R^{12} each independently is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{13} is selected from the group <u>consisting</u> of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally

substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;

~~R^{16} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$;~~

~~R^{17} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl;~~

~~R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, , OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, SOR^{17} and SO_2R^{17};~~

~~R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;~~

m is selected from the group <u>consisting</u> of 0, 1 and 2;

n is selected from the group <u>consisting</u> of 0, 1 and 2;

~~V is selected from the group of O and S;~~

W is selected from the group <u>consisting</u> of ~~O,~~ $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group <u>consisting</u> of O, ~~$S(O)_n$,~~ NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is ~~selected from the group of~~ O~~, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$~~;

and pharmaceutically acceptable salts thereof.

2. (Currently amended) A compound according to claim 1, wherein R^1 is selected from the group <u>consisting</u> of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

3. (Currently amended) A compound according to claim 2, wherein R^1 is selected from the group <u>consisting</u> of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

4. (Currently amended) A compound according to claim 3, wherein R^1 is selected from the group consisting of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl.

5. (Currently amended) A compound according to claim 1, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

6. (Currently amended) A compound according to claim 5, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

7. (Currently amended) A compound according to claim 6, wherein R^2 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl.

8. (Original) A compound according to claim 7, wherein R^2 is CF_3.

9. (Currently amended) A compound according to claim 1, wherein

R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

10. (Original) A compound according to claim 9, wherein R^3 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic ring.

11. (Currently amended) A compound according to claim 9, wherein R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

12. (Currently amended) A compound according to claim 1, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

13. (Currently amended) A compound according to claim 12, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl.

14. (Currently amended) A compound according to claim 13, wherein R^6 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

15. (Currently amended) A compound according to claim 12, wherein R^6 is selected from the group consisting of optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroaryl.

16. (Currently amended) A compound according to claim 1, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_2 - C_6$ alkenyl.

17. (Currently amended) A compound according to claim 16, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

18. (Currently amended) A compound according to claim 17, wherein R^5 is selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

19. (Original) A compound according to claim 18, wherein R^5 is hydrogen or CF_3.

20. (Currently amended) A compound according to claim 1, wherein R^7 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

21. (Currently amended) A compound according to claim 1, wherein R^8 is selected from the group consisting of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

22. (Original) A compound according to claim 21, wherein R^7 and R^8 are each hydrogen or optionally substituted $C_1 - C_2$ alkyl.

23. (Currently amended) A compound according to claim 1, wherein R^9 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

24. (Currently amended) A compound according to claim 23, wherein R^9 is selected from the group consisting of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

25. (Currently amended) A compound according to claim 1, wherein R^{10} is selected from the group consisting of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

26. (Currently amended) A compound according to claim 25, wherein R^{10} is selected from the group consisting of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$ and CO_2R^{12}.

27. (Currently amended) A compound according to claim 1, wherein R^4 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

28. (Currently amended) A compound according to claim 27, wherein R^4 is selected from the group consisting of hydrogen and optionally substituted $C_1 - C_2$ alkyl.

29. (Currently amended) A compound according to claim 1, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

30. (Currently amended) A compound according to claim 29, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally

substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkenyl and optionally substituted aryl; or

R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring.

31. (Currently amended) A compound according to claim 30, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

Claims 32 – 36 (Cancelled).

37. (Original) A compound according to claim 1, wherein m is 0 or 1.

38. (Original) A compound according to claim 37, wherein m is 1.

39. (Currently amended) A compound according to claim 1, wherein W is selected from the group consisting of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$.

40. (Original) A compound according to claim 39, wherein W is NH or $N\{R^{13}\}$.

41. (Currently amended) A compound according to claim 1, wherein X is selected from the group consisting of O, ~~S,~~ NH and $N\{R^{11}\}$.

42. (Currently amended) A compound according to claim 41, wherein X is O ~~or S~~.

43. (Canceled)

44. (Canceled)

45. (Currently amended) A compound according to claim 1, wherein Z is selected from the group consisting of NH, $N\{R^{11}\}$ and O.

46. (Original) A compound according to claim 45, wherein Z is NH or $N\{R^{11}\}$.

47. (Canceled)

48. (Canceled)

49. (Currently amended) A compound according to claim 1, wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl;

R^2 is selected from the group <u>consisting</u> of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl;

R^3 is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring;

R^5 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl;

R^6 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

50. (Currently amended) A compound according to claim 49, wherein:

R^7 is selected from the group <u>consisting</u> of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl;

R^8 is selected from the group <u>consisting</u> of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl; <u>and</u>

R^{13} is selected from the group <u>consisting</u> of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring. ~~ring; and~~

~~R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, C_1—C_4 alkyl, and optionally substituted C_1—C_4 haloalkyl~~.

51. (Currently amended) A compound according to claim 50, wherein:

m is 0 or 1;

W is selected from the group consisting of NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}};

X is selected from the group consisting of O, S, NH and N{R^{11}};

~~Y is O or S;~~ and

Z is selected from the group consisting of NH, N{R^{11}} and O.

Claims 52 – 55 (Cancelled).

56. (Currently amended) A compound ~~according to claim 1, wherein said compound is~~ selected from the group consisting of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one ;

(3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R/S*)-4-Ethyl-2,3,4,7-tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino-[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta-[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(6a*R*)-6a,7,8,9 -Tetrahydro-4-(trifluoromethyl)-1*H*,6*H*-pyrrolo[1',2':4,5][1,4]-oxazino[2,3-*f*]quinolin-2-one;

2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]-quinolin-8-one;

(3*R*)-8-Chloro-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(3*R*) -3-Ethyl-3,4-dihydro-8-isopropoxy-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; ~~and~~

(3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

a pharmaceutically acceptable salt thereof.

57. (Currently amended) A compound ~~according to claim 1, wherein said compound~~ ~~is~~ selected from the group consisting of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

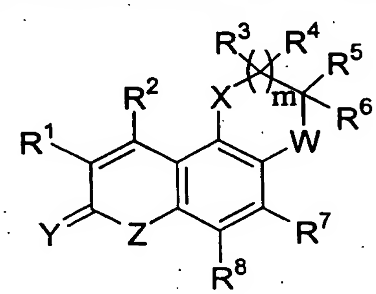
(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

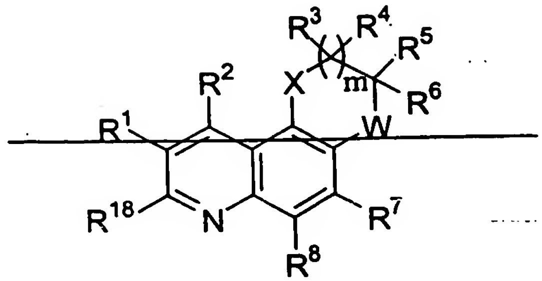
a pharmaceutically acceptable salt thereof.

58. (Currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



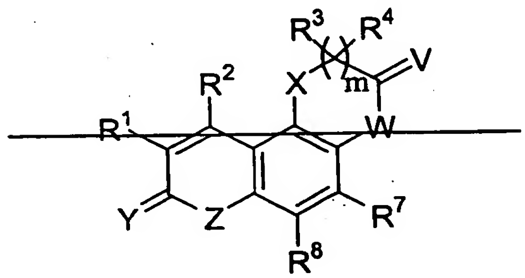
(I)

~~OR~~



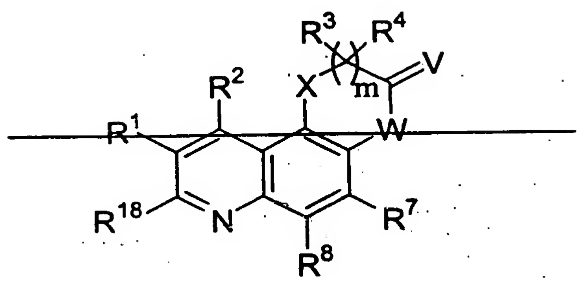
~~(II)~~

~~OR~~



~~(III)~~

~~OR~~



~~(IV)~~

wherein:

R^1 is selected from the group consisting of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl,

optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl;

R^3 and R^4 each independently is selected from the group consisting of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group consisting of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group consisting of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 -$ C_8 optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^8 is selected from the group <u>consisting</u> of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$;

R^9 is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{10} is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$;

R^{11} and R^{12} each independently is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl;

R^{13} is selected from the group <u>consisting</u> of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;

~~R^{16} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$;~~

~~R^{17} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl and optionally substituted $C_1 - C_8$ heteroalkyl;~~

~~R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, , OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, SOR^{17} and SO_2R^{17};~~

~~R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl;~~

m is selected from the group consisting of 0, 1 and 2;

n is selected from the group consisting of 0, 1 and 2;

~~V is selected from the group of O and S;~~

W is selected from the group consisting of ~~O,~~ $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}};

X and Z each independently is selected from the group consisting of O, ~~$S(O)_n$,~~ NH, N{R^{11}}, N{C(Y)R^{11}}, N{SO_2R^{12}} and N{S(O)R^{12}}; and

Y is ~~selected from the group of~~ O~~, S, N{R^{19}} and N{OR^{19}};~~

and pharmaceutically acceptable salts thereof.

59. (Original) A pharmaceutical composition according to claim 58, wherein said composition is suitable for enteral, parenteral, suppository or topical administration.

60. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^1 is selected from the group consisting of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

61. (Currently amended) A pharmaceutical composition comprising a compound according to claim 1, wherein R^2 is selected from the group consisting of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

62. (Currently amended) A pharmaceutical composition according to claim 59, wherein

R^1 is selected from the group consisting of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl; and

R^2 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl.

63. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^3 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

64. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^6 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

65. (Currently amended) A pharmaceutical composition according to claim 64, wherein R^6 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl.

66. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^5 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl.

67. (Currently amended) A pharmaceutical composition according to claim 66, wherein R^5 is selected from the group <u>consisting</u> of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

68. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^7 and R^8 each independently is selected from the group <u>consisting</u> of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

69. (Currently amended) A pharmaceutical composition according to claim 58, wherein

R^9 is selected from the group <u>consisting</u> of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, and optionally substituted $C_1 - C_6$ heteroalkyl; and

R^{10} is selected from the group <u>consisting</u> of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl.

70. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^4 is selected from the group consisting of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl.

71. (Currently amended) A pharmaceutical composition according to claim 58, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

72. (Currently amended) A pharmaceutical composition according to claim 71, wherein R^{13} is selected from the group consisting of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, and allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

73. (Canceled)

74. (Canceled)

75. (Original) A pharmaceutical composition according to claim 58, wherein m is 0 or 1.

76. (Currently amended) A pharmaceutical composition according to claim 58, wherein

W is selected from the group consisting of NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}};

and

X is selected from the group consisting of O, ~~S,~~ NH and N{R^{11}}.

77. (Currently amended) A pharmaceutical composition according to claim 58, wherein

~~Y is O or S; and~~

Z is selected from the group consisting of NH, N{R^{11}} and O.

Claims 78 – 107 (Cancelled).

REMARKS

This Amendment and Response is submitted in response to the Office Action, mailed May 3, 2005 (Office Action). A check for $1020 for the fee for a three-month extension of time accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Claims 1-30, 37-42, 45, 46, 49-51, 56-72 and 75-77 are pending. Claims 32-36, 43, 44, 47, 48, 52-55, 74, 74 and 80-107 are cancelled without prejudice or disclaimer. Applicant expressly reserves the right to pursue the cancelled subject matter in a continuing application. Claims 1-7, 9, 11-18, 20, 21, 23-31, 39, 41, 45, 49-51, 56-58, 60-72 and 76 are amended to recite more conventional claim language and to more distinctly claim the subject matter. Support for the amendment is found throughout the specification and, in particular, in the respective claims as originally filed.

Claims 1, 41, 42, 50, 51, 58 and 77 are amended to remove certain formulae and substituents in the definitions. Support for the amendment can be found throughout the specification, for example at page 17, line 8 through page 27, line 1 and in the claims as originally filed. Applicant expressly reserves the right to pursue the cancelled subject matter in a continuing application. Claims 56 and 57 are amended to be independent claims. No new matter has been added by reason of these amendments.

Informalities

Incorporation By Reference

The Examiner maintains the previous objection to the incorporation by reference of certain material in the specification (Office Action at page 2). Specifically, the Examiner alleges "anything incorporated by reference outside of the Background portion of the disclosure is assumed to be part of the invention and must be essential" (Office Action, page 3). The Examiner alleges that references at page 110, line 22 and at page 111, lines 25-26 describing the "co-transfection assay" constitute essential material. This rejection is respectfully traversed.

As pointed out in the previous Response, filed February 2, 2005, incorporation by reference of "essential material" and "nonessential material" is discussed in the MPEP at MPEP § 608.01(p)(I). For example, MPEP § 608.01(p)(I)(A) states:

> "Essential material" is defined as that which is "necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)" ...

In addition, Applicant respectfully submits that § 1.57(c) of the Patent Rules, directed to Incorporation by reference, defines "essential material" as material that is necessary to:

> (1) Provide a written description of the claimed invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and set forth the best mode contemplated by the inventor of carrying out the invention as required by the first paragraph of 35 U.S.C. 112;
> (2) Describe the claimed invention in terms that particularly point out and distinctly claim the invention as required by the second paragraph of 35 U.S.C. 112; or
> (3) Describe the structure, material, or acts that correspond to a claimed means or step for performing a specified function as required by the sixth paragraph of 35 U.S.C. 112.

All other material is considered "nonessential material" (see paragraph (d)). Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art. MPEP § 608.01(p)(I) also states that

> Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publictions....

The references objected to by the Examiner are Evans *et al.* on page 110, line 22, US Pat. Nos. 4,981,784 and 5,071,773 to Evans *et al.* on page 110, lines 25-26 and Berger *et al.* on page 111, lines 8-9. These references describe a co-transfection assay that mimics an *in vivo* system in the laboratory. None of the instant claims is directed to a co-transfection assay; the claims are directed to compounds and compositions. Assays are not claimed; nor is a particular assay required. Those of skill in the art can use any of a variety of known assays. The material incorporated by reference evidences this. Thus, the material incorporated by reference does not describe the "claimed invention" under MPEP § 608.01(p)(I)(A).

In addition, as previously submitted, the application describes the co-transfection assay and provides sufficient detail to allow one of skill in the art to practice the assay. The Examiner's attention is directed to the Biological Examples section of the application on page 110, line 20 through page 114, line 5. For example, Example B of the Biological Examples section, page 112, line through page 114, line, entitled Co-transfection assay, provides a detailed description of the assay. Hence, the material incorporated by reference is not required to provide an enabling disclosure, nor to describe the best mode (35 U.S.C. 112). Since the material incorporated by reference describes the state of the art and is not encompassed by the definition of "essential material" as set forth under MPEP § 608.01(p)(I)(A) or § 1.57(c) of the

Patent Rules, applicant respectfully submits that it is nonessential subject matter, under the definitions as set forth in § 1.57(c)-(d) of the Patent Rules.

In the Office Action, the Examiner states that "[t]he rule being advanced is that anything incorporated by reference outside of the Background portion of the disclosure is assumed to be part of the invention and must be essential" (Office Action at page 3). The Examiner suggests moving the passages containing incorporation by reference to the Background section in order to satisfy this "rule" (*Id*). Applicant is aware of no such "rule" and respectfully requests that the Examiner cite authority for it. The Examiner's attention is directed to § 1.57(b) of the Patent Rules, Incorporation by Reference, which states:

> (b) Except as provided in paragraph (a) of this section, an incorporation by reference must be set forth **in the specification** and must:
> (1) Express a clear intent to incorporate by reference by using the root words "incorporat(e)" and "reference" (e.g., "incorporate by reference"); and
> (2) Clearly identify the referenced patent, application, or publication. [emphasis added]

Under this Rule, an incorporation by reference must be set forth <u>in the specification</u>. There is no indication that all incorporations by reference outside of the Background section are to be deemed "essential subject matter."

A purpose for allowing material to be incorporated by reference is to minimize unnecessary bulk of patent application specifications. *See General Electric Co. v. Brenner,* 159 U.S.P.Q. 338 (D.C. Cir. 1968) (famously lamenting that "[f]iling cabinets abhor redundancy. Warehouses covet their space . . ."). Redundancy, whether in the background section or any other portion of the specification, may be avoided by incorporation by reference. The passage at issue describes an assay that can be used to characterize the subject matter, but which is not claimed. This is precisely the sort of information that can be incorporated by reference to avoid unwieldy applications. It also is appropriate to include the body of the specification in the section related to such assays where it assists the reader, rather than in the Background section as the Examiner insists.

Applicant further notes that the Examiner alleges that "Applicant's response also suggests that applicant presumes the right to determine for the USPTO what references are 'essential' and what references are not" (Action at page 3). Applicant acknowledges that the Office has "considerable discretion in determining what may or may not be incorporated by reference in a patent application" (MPEP § 608.01(p) (I)). Applicant must be fully responsive to an Office Action. Applicant respectfully submits that the traverse of the

objection included an analysis of incorporation by reference using the Patent Office's own rules as set forth in MPEP § 608.01(p)(I).

REJECTION OF CLAIMS 1-55, 58-77 AND 80-107 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH – SCOPE

Claims 1-55, 58-77 and 80-107 are rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter that was not described in the specification in such a way as to enable one of skill in the art to make and/or use the claimed subject matter because the scope is allegedly excessive in view of the disclosed exemplifications. The Examiner alleges that because the specification provides "only about 150 compounds" in the Examples section that the disclosure cannot be enabling for the entire scope of claimed compounds. The Examiner also alleges that some compounds that are encompassed by the claims are not "disclosed as having been synthesized within the examples," that none of the exemplary compounds discloses "a structure with the multiple layers of substituents on top of substituents provided by the claims" and that none of the examples "provides a complete description of how to make same."

Applicant respectfully traverses the rejection.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be satisfied by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything **within the scope** of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original.

The "invention" referred to in the enablement requirement of section 112 is the claimed subject matter. *Lindemann Maschinen-fabrik v. American Hoist and Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) ("The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention");

Raytheon Co. v. Roper Corp., 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 835, 225 USPQ 232 (1984).

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. . . it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with evidence or reasoning which is inconsistent with the contested statement.

Id. (emphasis in original); *See also Fiers v. Revel*, 984 F.2d 1164, 1171-72, 25 USPQ2d 1601, 1607 (Fed. Cir. 1993);, *Gould v. Mossinghoff*, 229 USPQ 1, 13 (D.D.C. 1985), *aff'd in part, vacated in part, and remanded sub nom. Gould v. Quigg*, 822 F.2d 1074, 3 USPQ2d 1302. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent , Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987).

The inquiry with respect to scope of enablement under 35 U.S.C. § 112, first paragraph, is whether it would require undue experimentation to make and use the subject matter as claimed. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); *see also In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

The starting point in an evaluation of whether the enablement requirement is satisfied is an analysis of each claim to determine its scope. The focus of the inquiry is whether everything within the scope of the claim is enabled. As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. *In re Moore*, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971). Once the scope of the claims is addressed, a determination must be made as to whether one

skilled in the art is enabled to make and use the entire scope of the claimed invention without undue experimentation.

The requirements of 35 USC §112, first paragraph, can be fulfilled by the use of illustrative examples or by broad terminology. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973):

> ... we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim .... What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

ANALYSIS

The Office Action fails to establish a prima facie case of lack of enablement pursuant to 35 U.S.C. § 112, first paragraph.

The test of enablement is not whether an example of everything within the scope of the claims is provided in the specification. The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue.

In the previous Action, the Examiner stated that the amount of direction provided is limited to the chemical synthesis of numerous [1,4]oxazino[2,3-*f*]quinolin-8-ones and data identifying which compounds are agonists or antagonists and alleges that no other chemical species has been disclosed as having been synthesized, isolated or subjected to any testing to determine possible medicinal activity. Applicant respectfully disagrees.

The specification teaches seven generic synthesis schemes (for example, see page 33, 35, 37, 38, 39, 41 and 42). The application names over 150 exemplary AR modulator compounds (for example, see page 29 through 32 and claims 56 and 57). The specification also provides over 50 working examples and two screening assays. It is respectfully submitted that the direction provided by the specification is sufficient to allow one of skill in the art to synthesize, test and administer any and all compounds of the claimed subject matter. One skilled in the art will recognize that the generic schemes may be used to synthesize such

compounds, though they also may be synthesized using other techniques known to those of skill in the art. Similarly, one of skill in the art may assess certain compounds of the present invention using the binding assay or the co-transfection assay, both of which are disclosed in the specification, though one of skill in the art may assess compounds using other known assays. Finally, administration of compounds is routine to one of skill in the medical arts.

Notwithstanding this, solely to expedite prosecution of this application, applicant has amended claims 1 and 58 to cancel formulae II, III, and IV, along with certain R-group substituents, without prejudice or disclaimer. Applicant asserts that the cancelled subject matter is fully enabled by the specification, as discussed above, in the traverse of the enablement rejection below and in the previous Response, and applicant reserves the right to pursue such subject matter in a continuing application.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

Within the "scope" rejection under 35 U.S.C. § 112, first paragraph, the Examiner suggests that "the term 'optionally substituted' <u>should be specifically defined</u> in the independent claims (claims 1 and 58)" Office Action at page 4 (emphasis in original); and again at page 7. Applicant respectfully submits that this rejection appears to be more appropriate under 35 U.S.C. § 112, second paragraph, where it also has been raised by the Examiner. Accordingly, this issue will be addressed more fully in the traverse under 35 U.S.C. § 112, second paragraph, below.

Applicant respectfully disagrees with the Examiner's explanation that "[a]nyone reading the original or the amended claims or both would not have otherwise known that 'hydroxyl' was an 'optional substituent.'" *Id.* Claims must be read in view of the specification. See e.g., MPEP § 2106 ("An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim."); MPEP § 608.01(o) ("The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification"); MPEP § 2173.05 ("When the specification states the meaning that a term in the claims is intended to have, the claim is examined using that meaning in order to achieve a complete exploration of the applicant's invention and its relation to the prior art."). The term "optionally substituted" is expressly defined in the specification. Thus, that definition will control interpretation of the term as it is used in the claim. Reciting the definition in the claims is unnecessary.

REJECTION OF CLAIMS 1-55, 58-77 AND 80-107 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH – ENABLEMENT

The Examiner separately rejects claims 1-55, 58-77, and 80-107 as allegedly not enabled. The Examiner identifies the *In re Wands* factors, which Applicants previously discussed in Response to the February Action, the content of which is repeated here by incorporation by reference. These factors will now be considered again.

As a preliminary matter, claims 80-107 are cancelled herein without prejudice or disclaimer. Applicant does not acquiesce to the rejection. The claims are cancelled in order to advance this application to allowance. Applicant reserves the right to pursue these claims in a continuing application.

ANALYSIS

Applying the above-noted factors to the instant facts reveals that the amount of experimentation is not undue.

1. **The scope of the claims.**

Claim 1 is directed to compounds of formula I and claims 2-57 ultimately depend from claim 1 and are directed to various embodiments thereof. Claim 58 is directed to pharmaceutical compositions including a pharmaceutically acceptable carrier and a compound of formula I, and claims 59-77 ultimately depend from claim 58 and are directed to various embodiments thereof.

The Examiner alleges that the "breadth of the compound claims is excessive," asserting that "the term 'may be optionally substituted' without specifying the substituents implied thereby renders the breadth excessive because said term implies that the unnamed substituents is/are open to all possible alternatives" (Office Action at page 5). Applicant respectfully points out that the term "optionally substituted" is defined in the specification at page 11 line 26 to page 12, line 9, which states:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

Thus, the recitation does not imply "that the unnamed substituents is/are open to all possible alternatives" as the Examiner asserts. The substituents include only those in the definition of the term.

B. Nature of the Invention

As amended, the claimed subject matter is directed to compounds of Formula I and pharmaceutical compositions that include compounds of Formula I. Claims 1-55 and 58-76 are directed to compounds as defined in the claims and to pharmaceutical compositions thereof.

C. State of the Art

The art of record shows that the skilled artisan can make and use the compounds of the present invention. In the present Action, the Examiner alleges that certain references are anticipatory prior art (Action at page 5) and other art is "very close" (Action at page 8). Although applicant traverses the art rejection below, applicant agrees that the prior art is replete with references that show that the skilled artisan can use known organic synthesis scheme and reactions to produce various bicyclic, tricyclic and polycyclic organic compounds, including, for example, quinolines, quinolinones, coumarins, benzoxyzins, oxazolidines, azasteroids, progesterones, azachlormadinones, anthrasteroids, flutamides and phthalimides. The Examiner asserts that "The state of the prior art is defined by the prior art presently cited by applicant and by examiner." Applicant is not aware of that definition and respectfully requests that the Examiner cite authority.

D. Level of Skill in the Art

The Examiner states that the skill in the art of chemical synthesis is high. Applicant agrees with this assessment. That skill, together with the instant specification and the known art, allow the skilled artisan to make any and all of the claimed compounds. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

The Examiner notes that "the level of skill in the medicinal arts is moderate because it is unclear which if any of the compounds disclosed herein are active against one or more specific disease conditions." Office Action at page 5. Applicant respectfully disagrees. The level of skill in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further

evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

E. Level of Pedictability

The art of chemical synthesis is predictable and is dictated by recognized chemical reactions and constraints. The medical arts are also predictable, in that various assays and models that mimic an *in vivo* system in the laboratory were available and known to the skilled artisan at the time of filing of the application. For example, see U.S. Pat. No. 5,071,773 to Evans *et al.* (1991), which teaches a bioassay for evaluating whether compounds are functional ligands for receptor proteins. Such assays are routine in the medical arts. Thus, it is not necessary that one skilled in the art be able to predict which compound will be most active for a particular medical application. The specification, in view of the skill in the art, describes how to make and administer, and if necessary test, any claimed compound. As discussed above, the level of knowledge and skill in the preparation, isolation and manipulation of compounds was high as of the filing date of the instant application. Thus, in view of the teachings of the specification, in combination with what was known at the time the original application was filed, applicant respectfully submits that the claimed compounds can be prepared predictably using any methods disclosed in the specification or that are known to those skilled in this art. Further, formulating such compounds into a pharmaceutical composition and administration of such compositions to a subject is well know in the medical arts. Thus, preparation and administration of pharmaceutical compounds is also predictable.

F. Amount of Direction Provided

The Examiner alleges that the direction provide by the specification is limited to the chemical syntheses of [1,4]oxazino[2,3-*f*]-quinolin-8-ones and providing data identifying which compounds are antagonists and which are agonists of known androgen receptors. Applicant respectfully disagrees. The specification provides a general description of non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists (i.e., partial activators and/or tissue-specific activators) and antagonists for androgen receptors. The application discloses compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and pharmaceutical compositions for modulating processes mediated by steroid receptors. The application names over 150 exemplary compounds (for example, see page 29 through 32 and claims 56 and 57). The application also discloses methods of making such compounds as well as intermediates used in their synthesis, providing seven generic synthesis schemes (for example, see page 33, 35,

37, 38, 39, 41 and 42). One of skill in the art can readily follow these schemes or known variations of such schemes with any of a vast number of commonly available starting materials to arrive at the full scope of the claimed subject matter.

G. Working Examples

The specification provides synthesis schemes and over 50 working examples directed to chemical methods of preparing compounds within the scope of the claims. The application names over 150 exemplary compounds. The specification also provides biological examples for testing and using the compounds, including the co-transfection assay and binding assay and results of analysis of exemplary compounds.

Hence the specification provides a variety of examples of compounds that fall within the scope of the claims evidencing that the claimed compounds function as claimed. The specification also provides two screening assays. As discussed above, various screening assays for assessing the ability of a compound or composition to modulate the transcriptional ability of intracellular receptors are known to those of skill in the art, such as those described in U.S. Pat. Nos. 4,981,784, 5,071,773, 5,298,429, and 5,506,102 and in WO89/05355, WO91/06677, WO92/05447, WO93/11235, WO93/23431, WO94/23068, WO95/18380 and CA 2,034,220. The requirements of 35 U.S.C. §112, first paragraph, do not require a specific example of everything within the scope of the claims. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973).

H. Quantity of Experimentation Required

The direction provided by the specification is sufficient to allow one of skill in the art to synthesize, test and administer any and all compounds of the invention as claimed. One skilled in the art will recognize that the generic schemes may be used to synthesize such compounds, though they also may be synthesized using techniques known to those of skill in the art. Similarly, one of skill in the art may assess certain compounds of the present invention using the binding assay or the co-transfection assay, both of which are disclosed in the specification, though one of skill in the art may assess compounds using other known assays. Finally, administration of compounds is routine to one of skill in the medical arts.

The Examiner states, "the quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive because the instant specification only discloses how to make compounds with a [1,4]oxazino[2.3-*f*]isoquinolin-8-one ring system . . ." Office Action at page 5. Applicant respectfully disagrees. The generic synthesis schemes provided in the specification enable one of skill in the art to prepare far more

compounds than the Examiner admits. There is nothing of record to suggest that the synthesis of any of the claimed compounds or compositions would require development of new procedures or excessive experimentation. Organic synthesis methods have been used for decades. Those of skill in the art, provided the synthesis schemes in the specification and known in the art, can readily synthesize compounds encompassed by the claims using routine experimentation and available starting materials.

As discussed above, bioassays for evaluating whether compounds are functional ligands for receptor proteins were known in the art since at least 1991. Such assays are routine in this art and do not require excessive experimentation. It is noted that the test for undue experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine. . ." *In re Wands* 858 F.3d 731, 737 (Fed Cir. 1988). Thus, methods for making and evaluating androgen receptor modulator compounds were available and known to skilled artisans at the time of filing the application. Those skills, together with the teaching of the specification, including cited and incorporated references, allow the skilled artisan to make any and all of the claimed compounds. As discussed previously, it is not necessary that one skilled in the art be able to predict which compound will be most active for a particular medical application. The specification, in view of the skill in the art, enables one to make and administer, and if necessary test, any claimed compound.

CONCLUSION

In light of the scope of the claims, the teachings in the specification, the high level of skill of those in this art, the working examples, and the extensive knowledge of those of skill in this art, it would not require undue experimentation for a person skilled in the art to make and use the claimed compounds and compositions. Accordingly, the applicant respectfully submits that all of the claims are fully enabled by the specification in view of the state of the art at the time of filing. Applicant respectfully requests reconsideration and withdrawal of all rejections under 35 U.S.C. § 112, first paragraph.

Policy Considerations

The Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. Moreover, it is unfair, unduly limiting and contrary to the public policy and constitutional mandate that underlie the U.S. patent system to require applicant to limit the instant claims to the compounds specifically discussed in the examples. To do so permits one of skill in this art to

practice the disclosed invention but avoid liability for infringement merely by selecting a species of the disclosed genus not specifically discussed in the examples.

As a broad body of knowledge is available in the area of chemical, it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to the particular exemplary embodiments. See, e.g., *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. To permit that is simply not fair. The instant application in light of the knowledge of those of skill in the art provides adequate guidance for making and using androgen receptor modulator compounds and compositions. Having done so, it is now routine for others to make minor modifications by any method known in this art. Those of skill in the art should not be permitted to make minor modifications, such as selecting a compound not specifically disclosed in the examples, to avoid infringing such claims.

REBUTTAL TO EXAMINER'S ARGUMENTS

<u>Claims 85, 89, 93, 101 and 107</u>

Beginning at page 7 of the Office Action, the Examiner discusses some remarks made by applicants in the previous Response. In that discussion, the Examiner appears to reject claims 85, 89, 93, 101 and 107 on additional grounds. Applicants do not acquiesce to any of these grounds. However, since claims 80-107 are cancelled without prejudice or disclaimer, Applicants do not address these additional grounds, but reserve the right to pursue these claims in a continuing application.

<u>"Compound and Pharmaceutical Composition Claims"</u>

The Examiner alleges certain generalities regarding the "compound and pharmaceutical composition claims" (see Office Action at page 8). The Examiner asserts that

certain unidentified terms (aryl, arylalkyl, heteroaryl, etc.) are allegedly incompletely defined and "typically" possess any of a number of alleged flaws selected from among:

i) lack any upper bounds as to size,

and when heteroatoms are suggests said terms

ii) fail to define which hetero atoms are to be selected from
iii) the number of said heteroatoms, or
iv) the location(s) or the ring system(s) containing said heteroatom(s) and
v) because a proper definition of "optionally substituted" is not present in any independent claim.

The Examiner did not identify all of the claims against which this "enablement rejection" is applied, nor to which terms of the claims the rejection is applied. Applicant requests that the Examiner more fully articulate the rejection so that the applicant can be fully responsive. In order to advance the prosecution of this application, applicant provides the following traverse.

The terms identified by the Examiner are specifically defined in the specification. For example, the definition for "aryl" is recited on page 9,line 26 through page 10, line 5, which recites:

> The term "aryl," alone or in combination, refers to an optionally substituted aromatic ring system. The term aryl includes monocyclic aromatic rings, polyaromatic rings and polycyclic aromatic ring systems containing from six to about twenty carbon atoms. The term aryl also includes monocyclic aromatic rings, polyaromatic rings and polycyclic ring systems containing from 6 to about 12 carbon atoms, as well as those containing from 6 to about 10 carbon atoms. The polyaromatic and polycyclic aromatic rings systems may contain from two to four rings. Examples of aryl groups include, without limitation, phenyl, biphenyl, naphthyl and anthryl ring systems.

The definition for "arylalkyl" is recited on page 11, lines 9-11, which recites:

> The term "arylalkyl," alone or in combination, refers to an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as, for example, benzyl, 2-phenylethyl and the like.

The definition for "heteroaryl" is recited on page 10, lines 6-19, which recites:

> The term "heteroaryl" refers to optionally substituted aromatic ring systems containing from about five to about 20 skeletal ring atoms and having one or more heteroatoms such as, for example, oxygen, nitrogen and sulfur. The term heteroaryl also includes optionally substituted aromatic ring systems having from 5 to about 12 skeletal ring atoms, as well as those having from 5 to about 10 skeletal ring atoms. The term heteroaryl may include five- or six-membered heterocyclic rings, polycyclic heteroaromatic ring systems and polyhetero-aromatic ring systems where the ring system has two, three or four rings. The terms heterocyclic, polycyclic heteroaromatic and polyheteroaromatic include ring systems containing optionally substituted heteroaromatic rings having more than one heteroatom as described above (e.g., a six membered ring with two

> nitrogens), including polyheterocyclic ring systems of from two to four rings. The term heteroaryl includes ring systems such as, for example, furanyl, benzofuranyl, chromenyl, pyridyl, pyrrolyl, indolyl, quinolinyl, N-alkyl pyrrolyl, pyridyl-N-oxide, pyrimidoyl, pyrazinyl, imidazolyl, pyrazolyl, oxazolyl, benzothiophenyl, purinyl, indolizinyl, thienyl and the like.

Applicant respectfully points out that the term "optionally substituted" is defined in the specification at page 11, line 26 to page 12, line 9, which states:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

As discussed in more detail below in the traverse of the rejection under 35 U.S.C. § 112, second paragraph, where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. The claims are read in light of the specification, and the meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification.

Applicants respectfully request that the Examiner reconsider and withdraw this rejection or, in the alternative, identify which claims and terms are subject to this rejection to afford the applicant an opportunity to properly respond with particularity.

REJECTION OF CLAIMS 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that the recitation "selected from the group of" is incomplete because Markush groups are properly formulated to recite "selected from the group consisting of" (Office Action at page 6).

The rejection is obviated by the amendment of claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 herein.

REJECTION OF CLAIMS 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that the recitation "optionally substituted" fails "to specify the substituents implied thereby" (Office Action at pages 9). The Examiner admits that the definition for the recitation "optionally substituted" is found within the specification but states that he "fails to understand why this definition is not found in the independent claims" (Office Action at page 7). The Examiner further alleges that the definition "does not meet the requirements of the statute because for a number of reasons said definition fails to have adequately defined metes and bounds (35 USC §112, 2nd ¶)."

Applicant respectfully traverses the rejection. The term "optionally substituted" is defined in the specification at page 11, line 26 to page 12, line 9, which states:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., $-CH_2CF_3$).

Thus, the recitation "optionally substituted" does not imply "that the unnamed substituents is/are open to all possible alternatives" as alleged by the Examiner. As discussed above, claims must be read in view of the specification. See e.g., MPEP § 2106 ("An applicant is entitled to be his or her own lexicographer, and in many instances will provide an explicit definition for certain terms used in the claims. Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim."); MPEP § 608.01(o) ("The meaning of every term used in any of the claims should be apparent from the descriptive portion of the specification"); MPEP § 2173.05 ("When the specification states the meaning that a term in the claims is intended to have, the claim is examined using that meaning in order to achieve a complete exploration of the applicant's

invention and its relation to the prior art."). The term "optionally substituted" is expressly defined in the specification. Thus, reciting that definition in the claims is not necessary.

Furthermore, the USPTO recognizes the use of this term in patent claims. A search of the USPTO database for the time period 1976 to present for patents with the recitation "optionally substituted" in the claims yielded 22,359 patents. While applicant realizes that the prosecution history of one patent is not relevant to another, the widespread use of the recitation "optionally substituted" in claims evidences that one of skill in the art understands the meaning of this term.

The Examiner alleges that "for a number of reasons" the definition in the specification allegedly "does not meet the requirements of the statute" or "fails to have adequately defined metes and bounds (35 USC §112, 2nd ¶)" (Office Action at page 7). The Examiner does not provide an explanation of these "number of reasons." Applicant respectfully requests that the Examiner withdraw the rejection or, in the alternative, more fully articulate the "number of reasons" so that applicant is afforded the opportunity to more fully address the issue.

REJECTION OF CLAIMS 1 and 58 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that claiming " 'C_1-C_8 heteroalkyl' and 'OR^9' are directed to substantially overlapping subject matter; i.e., the latter is entirely encompassed by the former." Applicant respectfully traverses the rejection. According to the MPEP:

> [T]he double inclusion of an element by members of a Markush group is not, in itself sufficient basis for objection to or rejection of claims. . . . For example, the Markush group, 'selected from the group consisting of amino, halogen, nitro, chloro and alkyl' should be acceptable even though 'halogen' is generic to 'chloro.'"

MPEP, § 2173.05(h). Thus even if OR^9 were, as the Examiner asserts, "completely encompassed" by the term "C_1-C_8 heteroalkyl," a rejection on that basis would be improper. Moreover, "OR^9" is not, in fact, completely encompassed by "C_1-C_8 heteroalkyl." By way of non-limiting example, R^9 may be hydrogen. Thus, OR^9 may be OH, which is not a C_1-C_8 heteroalkyl. Applicants respectfully submit that this rejection is improper, both legally and factually, and should be withdrawn.

REJECTION OF CLAIMS 87-107 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 87-107 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicant regards as the invention because the Examiner alleges that the term "modulate" is "indefinite for failing to indicate what specific treatment action(s) or effect(s) is(are) intended."

Without a acquiescing to the Examiner's allegation and solely to expedite prosecution, claims 87-107 are cancelled herein without prejudice or disclaimer. Thus, the rejection as applied to claims 87-107 under 35 U.S. C. § 102 is moot.

REJECTION OF CLAIMS 1-7, 12-14, 16-18, 20-26, 32-34, 37, 41-46, 49-53, 58-62, 64-70, 73, 75 and 77 UNDER 35 U.S.C. §102(b)

Claims 1-7, 12-14, 16-18, 20-26, 32-34, 37, 41-46, 49-53, 58-62, 64-70, 73, 75 and 77 are rejected under 35 U.S.C. § 102(b) as anticipated by Kyotani *et al*. because Kyotani *et al.* allegedly discloses compounds that include all the limitations of the claimed subject matter. The Examiner alleges that the instant claims are anticipated by compounds of structure "(1e)" at column 3 in the reference.

This rejection is respectfully traversed.

RELEVANT LAW

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. *See, also, Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), *cert. denied*, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on the Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

THE CLAIMS

Claim 1 is directed to compounds of formula (I), where W is $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}$ or $N\{SO_2R^{11}\}$, X and Z each independently is O, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$,

N{SO_2R^{12}} or N{S(O)R^{12}}, and Y is O. Claims 2-31, 37-42, 45, 46, 49-51 and 61 depend from claim 1. Claim 58 is directed to pharmaceutical compositions that includes a pharmaceutically acceptable carrier and a compound of formula (I), where W is $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}}, X and Z each independently is O, NH, N{R^{11}}, N{C(Y)R^{11}}, N{SO_2R^{12}} or N{S(O)R^{12}}, and Y is O. Claims 59, 60, 62-72 and 75-77 depend from claim 58.

Disclosure of Kyotani *et al.* (US 5,576,324)

Kyotani *et al.* discloses quinolinone derivatives and medicinally acceptable salts thereof that have positive inotropic action, antiarrhythmic action and vasodilating action. Kyotani *et al.* discloses compounds of formula (1e), where the 6 position of the quinolinone core structure contains an oxygen substituent.

Differences between Kyotani *et al* and the Claimed Subject Matter

The 6 position of the core structure in formula (1e) corresponds to W in formula (I) in instant claims 1 and 58. Formula (1e) of Kyotani *et al.* does not contain $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}} in the 6 position of the quinolinone core structure. Thus, Kyotani *et al.* does not disclose compounds of formula (I), where W is $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}}. Absent such a disclosure, Kyotani *et al.* does not disclose every element of the claimed subject matter, and thus does not anticipate claims 1 and 58. Thus, claims 2-31, 37-42, 45, 46, 49-51 and 61, which depend from claim 1, and claims 59, 60, 62-72 and 75-77, which depend from claim 58, are not anticipated by Kyotani *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

REJECTION OF CLAIMS 1-7, 9, 11-14, 16-18, 20, 25-28, 32-34, 37, 38, 41, 42, 45, 46, 49, 52, 53, 58-62, 64-70 and 76 UNDER 35 U.S.C. §102(b)

Claims 1-7, 9, 11-14, 16-18, 20, 25-28, 32-34, 37, 38, 41, 42, 45, 46, 49, 52, 53, 58-62, 64-70 and 76 are rejected under 35 U.S.C. § 102(b) as anticipated by LaMontagne *et al.* because LaMontagne *et al.* allegedly discloses compounds that include all the limitations of the claimed subject matter. The Examiner alleges that the instant claims are anticipated by structures 4k-4k on page 965, compounds 2d and 2e on page 966, compounds 3f-3g on page 966 and compounds 4h-4k on page 967 of LaMontagne *et al.*.

This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

Disclosure of LaMontagne *et al.*

LaMontagne *et al.* discloses the synthesis and biological activity of 5-alkoxy analogues of 4-methylprimaquine. The compounds disclosed by LaMontagne *et al.* are substituted quinolines.

Differences between LaMontagne *et al.* and the Claimed Subject Matter

Formula (I) of claims 1 and 58 does not encompass quinoline compounds. LaMontagne *et al.* does not disclose compounds of formula (I). Absent such a disclosure, LaMontagne *et al.* does not disclose every element of the claimed subject matter and therefore does not anticipate claims 1 and 58. Claims 2-31, 37-42, 45, 46, 49-51 and 61 depend from claim 1, and claims 59, 60, 62-72 and 75-77 depend from claim 58. Hence, LaMontagne *et al.* does not anticipate any of claims 1-7, 9, 11-14, 16-18, 20, 25-28, 32-34, 37, 38, 41, 42, 45, 46, 49, 52, 53, 58-62, 64-70 and 76. Reconsideration and withdrawal of the rejection are respectfully requested.

REJECTION OF CLAIMS 1-7, 9, 11-14, 16-18, 20, 21, 37, 38, 41-45, 49, 52, 58-68, 70, 75 and 77 UNDER 35 U.S.C. §102(b)

Claims 1-7, 9, 11-14, 16-18, 20, 21, 37, 38, 41-45, 49, 52, 58-68, 70, 75 and 77 are rejected under 35 U.S.C. § 102(b) as anticipated by Debenedetti *et al.* because the reference allegedly discloses compounds that include all the limitations of the claimed subject matter. The Examiner alleges that the instant claims are anticipated by compounds 1 and 3 on page 701 of Debenedetti *et al.* This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

Disclosure of Debenedetti *et al.*

Debenedetti *et al.* discloses three 5,6,7-trioxygenated coumarins that are isolated from the aerial parts of *Pterocaulon virgatum*(L.) DC. and *Pterocaulon purpurascens* Malme. Specifically, Debenedetti *et al.* discloses isopurpurasol (compound **1**), its regiosomer (compound **3**) and purpuraol (compound **2**).

Differences between Debenedetti *et al.* and the Claimed Subject Matter

The three compounds disclosed by Debenedetti *et al.* contain an oxygen substituent at the 6 position of the coumarin core structure, which corresponds to W in instant formula (I). The compounds disclosed by Debenedetti *et al.* do not contain $S(O)_n$, NH, $N\{R^{13}\}$,

N{C(Y)R^{11} or N{SO_2R^{11}} in the 6 position of the coumarin core structure. Thus Debenedetti *et al.* does not disclose compounds of formula (I) where W is $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}}. Absent such a disclosure, Debenedetti *et al.* does not disclose every element of the claimed subject matter and thus does not anticipate claim 1 or claim 58. Claims 2-31, 37-42, 45, 46, 49-51 and 61 depend from claim 1, and claims 59, 60, 62-72 and 75-77 depend from claim 58. Because Debenedetti *et al.* does not anticipate claims 1 or 58, Debenedetti *et al.* does not anticipate any of claims 1-7, 9, 11-14, 16-18, 20, 21, 37, 38, 41-45, 49, 52, 58-68, 70, 75 and 77. Reconsideration and removal of the rejection are respectfully requested.

REJECTION OF CLAIMS 1-7, 12-14, 16-18, 20, 21, 23, 24, 37, 41-45, 49, 50, 52, 58-62, 64-68, 70, 73, 75 and 77 UNDER 35 U.S.C. §102(b)

Claims 1-7, 12-14, 16-18, 20, 21, 23, 24, 37, 41-45, 49, 50, 52, 58-62, 64-68, 70, 73, 75 and 77 are rejected under 35 U.S.C. § 102(b) as anticipated by Castillo *et al.* because Castillo *et al.* allegedly discloses compounds and pharmaceutical compositions that include all the limitations of the claimed subject matter. This rejection is respectfully traversed.

RELEVANT LAW

See related section above.

THE CLAIMS

See related section above.

Disclosure of Castillo *et al.*

Castillo *et al.* discloses a method for the synthesis of methylenedioxycoumarins. Castillo *et al.* discloses the synthesis and characterization of six methylenedioxycoumarins, namely compounds **3**, **4**, **5**, **6**, **7** and **8**. The Examiner alleges that compound **6** falls within the scope of the instant claims and thus anticipates the claimed subject matter.

Differences between Castillo *et al.* and the claimed Subject Matter

Compound 6 of Castillo *et al.* contains an oxygen substituent at the 6 position of the coumarin core structure, which corresponds to W in formula (I). Compound **6** does not contain $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}} in the 6 position of the coumarin core structure. Therefore, Castillo *et al.* does not disclose compounds of formula (I), where W is $S(O)_n$, NH, N{R^{13}}, N{C(Y)R^{11} or N{SO_2R^{11}}. Absent such a disclosure, Castillo *et al.* does not disclose every element of claims 1 and 58. Claims 2-31, 37-42, 45, 46, 49-51 and 61 depend from claim 1, and claims 59, 60, 62-72 and 75-77 depend from claim 58. Thus, Castillo *et al.* does not anticipate any of claims 1-7, 12-14, 16-18, 20, 21, 23, 24, 37, 41-45,

49, 50, 52, 58-62, 64-68, 70, 73, 75 and 77. Reconsideration and withdrawal of the rejection and respectfully requested.

* * *

In view of the above, reconsideration and allowance is respectfully requested.

Respectfully submitted,

Stephanie Seidman
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Confirmation No.: 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHOD**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Dear Sir:

Responsive to the Office Action, mailed July 29, 2004, entry of the following amendments and consideration of the following remarks are respectfully requested.

Amendments to the specification begin on page 2 of this paper.

Amendments to the claims are reflected in the listing of the claims which begin on page 3 of this paper.

Remarks/Arguments begin on page 31 of this paper.

Supporting Documents are provided herewith.

A **supplemental Information Disclosure statement** (IDS) accompanies this response.

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
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I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Stephanie Seidman

AMENDMENTS TO THE SPECIFICATION:

Please correct the name of the compound provided in Example 35 at page 83, lines 2-4 as follows:

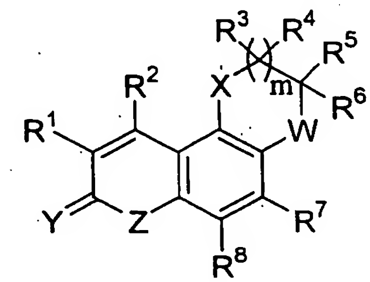
7,7a,8,9,10,10a-Hexahydro-7-(2,2,2-trifluoroethyl)1-(trifluoromethyl)--4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*] ~~quinolin-3-one~~ quinolin-8-one (Compound **135**, Structure **11** of **Scheme II**, where R^1, R^4, R^5, = H, R^2 = trifluoromethyl, R^3, R^6 = $-CH_2CH_2CH_2-$, R^{13} = CH_2CF_3)

AMENDMENTS TO THE CLAIMS:

Please amend claims 1 -3, 5-7, 9, 11-18, 20-21, 23, 25, 27, 29-30, 32, 35, 49-50, 58, 60-74, 80-88, and 90-107 as follows. Please cancel claims 78 and 79 without prejudice or disclaimer. This listing of claims replaces all prior versions, and listings of claims, in the application.

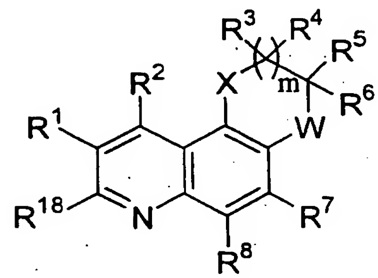
LISTING OF CLAIMS:

1. (currently amended) A compound having the formula:



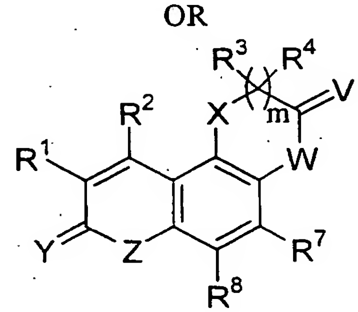
(I)

OR



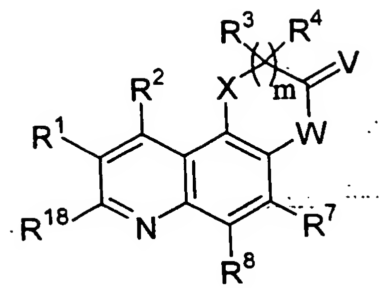
(II)

OR



(III)

OR



(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently ~~are~~ is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted~~;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted~~;

R^9 is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl~~;~~

~~wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted~~;

R^{10} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted~~;

R^{11} and R^{12} each independently is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted;

R^{13} is selected from the group of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~;

R^{16} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{17} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl and $C_1 - C_8$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, $\cancel{C_1 - C_8 \text{ heteroalkyl}}$, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, $\cancel{COR^{17}}$, $\cancel{CO_2R^{17}}$, $\cancel{CONR^{16}R^{17}}$, SOR^{17} and SO_2R^{17}~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 -$

C_8 cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is selected from the group of O, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$;

and pharmaceutically acceptable salts thereof, wherein the compound is a modulator for a member of the androgen receptor family.

2. (currently amended) A compound according to claim 1, wherein R^1 is selected from the group of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

3. (currently amended) A compound according to claim 2, wherein R^1 is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

4. (original) A compound according to claim 3, wherein R^1 is selected from the group of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl.

5. (currently amended) A compound according to claim 1, wherein R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

6. (currently amended) A compound according to claim 5, wherein R^2 is selected from the group of hydrogen, F, Cl, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$

alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

7. (currently amended) A compound according to claim 6, wherein R^2 is selected from the group of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

8. (original) A compound according to claim 7, wherein R^2 is CF_3.

9. (currently amended) A compound according to claim 1, wherein

R^3 is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

10. (original) A compound according to claim 9, wherein R^3 and R^6 taken together form a four to six membered saturated or unsaturated carbocyclic ring.

11. (currently amended) A compound according to claim 9, wherein R^3 is selected from the group of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

12. (currently amended) A compound according to claim 1, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~.

13. (currently amended) A compound according to claim 12, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally

substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl~~, wherein the alkyl, heteroalkyl, haloalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

14. (currently amended) A compound according to claim 13, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

15. (currently amended) A compound according to claim 12, wherein R^6 is selected from the group of optionally substituted aryl, optionally substituted arylalkyl and optionally substituted heteroaryl~~, wherein the aryl, arylalkyl and heteroaryl groups may be optionally substituted~~.

16. (currently amended) A compound according to claim 1, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

17. (currently amended) A compound according to claim 16, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

18. (currently amended) A compound according to claim 17, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

19. (original) A compound according to claim 18, wherein R^5 is hydrogen or CF_3.

20. (currently amended) A compound according to claim 1, wherein R^7 is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted~~.

21. (currently amended) A compound according to claim 1, wherein R^8 is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl, groups may be optionally substituted~~.

22. (original) A compound according to claim 21, wherein R^7 and R^8 are each hydrogen or optionally substituted $C_1 - C_2$ alkyl.

23. (currently amended) A compound according to claim 1, wherein R^9 is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

24. (original) A compound according to claim 23, wherein R^9 is selected from the group of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

25. (currently amended) A compound according to claim 1, wherein R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

26. (original) A compound according to claim 25, wherein R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$ and CO_2R^{12}.

27. (currently amended) A compound according to claim 1, wherein R^4 is selected from the group of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

28. (original) A compound according to claim 27, wherein R^4 is selected from the group of hydrogen and optionally substituted $C_1 - C_2$ alkyl.

29. (currently amended) A compound according to claim 1, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted

heteroarylalkyl~~, wherein the alkyl, cycloalkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

30. (currently amended) A compound according to claim 29, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkenyl and optionally substituted aryl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl and aryl groups may be optionally substituted~~; or

R^6 and R^{13} taken together form a five to six membered saturated or unsaturated heterocyclic ring.

31. (original) A compound according to claim 30, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

32. (currently amended) A compound according to claim 1, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$ alkyl, and optionally substituted $C_1 - C_4$ haloalkyl ~~and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

33. (original) A compound according to claim 32, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16} and $NR^{16}R^{17}$.

34. (original) A compound according to claim 33, wherein R^{18} is selected from the group of hydrogen, F, Cl and OR^{16}.

35. (currently amended) A compound according to claim 1, wherein R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

36. (original) A compound according to claim 35, wherein R^{19} is selected from the group of hydrogen and optionally substituted $C_1 - C_4$ alkyl.

37. (original) A compound according to claim 1, wherein m is 0 or 1.

38. (original) A compound according to claim 37, wherein m is 1.

39. (original) A compound according to claim 1, wherein W is selected from the group of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$.

40. (original) A compound according to claim 39, wherein W is NH or $N\{R^{13}\}$.

41. (original) A compound according to claim 1, wherein X is selected from the group of O, S, NH and $N\{R^{11}\}$.

42. (original) A compound according to claim 41, wherein X is O or S.

43. (original) A compound according to claim 1, wherein Y is O or S.

44. (original) A compound according to claim 43, wherein Y is O.

45. (original) A compound according to claim 1, wherein Z is selected from the group of NH, $N\{R^{11}\}$ and O.

46. (original) A compound according to claim 45, wherein Z is NH or $N\{R^{11}\}$.

47. (original) A compound according to claim 1, wherein V is S.

48. (original) A compound according to claim 1, wherein V is O.

49. (currently amended) A compound according to claim 1, wherein:

R^1 is selected from the group of hydrogen, F, Cl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, <u>optionally substituted</u> $C_1 - C_4$ alkyl, <u>optionally substituted</u> $C_1 - C_4$ haloalkyl and <u>optionally substituted</u> $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, <u>optionally substituted</u> $C_1 - C_6$ alkyl, <u>optionally substituted</u> $C_1 - C_6$ haloalkyl, <u>optionally substituted</u> $C_1 - C_6$ heteroalkyl, <u>optionally substituted</u> $C_2 - C_6$ alkynyl and <u>optionally substituted</u> $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~;

R^3 is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring;

R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~;

R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

50. (currently amended) A compound according to claim 49, wherein:

R^7 is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^8 is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and

optionally substituted heteroarylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl groups may be optionally substituted~~; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring; and

R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$ alkyl, and optionally substituted $C_1 - C_4$ haloalkyl ~~and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl, heteroalkyl groups may be optionally substituted~~.

51. (original) A compound according to claim 50, wherein:

m is 0 or 1;

W is selected from the group of NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X is selected from the group of O, S, NH and $N\{R^{11}\}$;

Y is O or S; and

Z is selected from the group of NH, $N\{R^{11}\}$ and O.

52. (original) A compound according to claim 1, wherein said compound is represented by formula (I).

53. (original) A compound according to claim 1, wherein said compound is represented by formula (II).

54. (original) A compound according to claim 1, wherein said compound is represented by formula (III).

55. (original) A compound according to claim 1, wherein said compound is represented by formula (IV).

56. (original) A compound according to claim 1, wherein said compound is selected from the group of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3,4-dimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3,4-Diethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one ;

(3*R*)-4-Allyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-isobutyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-4-methyl-3-propyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-4-Ethyl-2,3,4,7-tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R/S*)-2,3,4,7-Tetrahydro-3-propyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-methyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Ethyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Allyl-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-phenyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-phenyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Benzyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-Tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-3-isopropoxy-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(6a*R*)-6a,7,8,9 -Tetrahydro-4-(trifluoromethyl)-1*H*,6*H*-pyrrolo[1',2':4,5][1,4]oxazino[2,3-*f*]quinolin-2-one;

2,3,4,7-Tetrahydro-2,2,4-trimethyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-8-Chloro-3-ethyl-3,4-dihydro-8-isopropoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(3*R*) -3-Ethyl-3,4-dihydro-8-isopropoxy-8-methoxy-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-2*H*-[1,4]oxazino[2,3-*f*]quinoline;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(−)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-methyl-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Ethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(-)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(+)-2,3,4,7-Tetrahydro-3,4-bis(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-4-Cyclopropylmethyl-2,3,4,7-tetrahydro-3-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-Cyclopropylmethyl-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-2-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-4-(2-hydroxy-2-methylpropyl)-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one; and

(3*R*)-2,3,4,7-Tetrahydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one.

57. (original) A compound according to claim 1, wherein said compound is selected from the group of:

(3*R*)-2,3,4,7-Tetrahydro-3-methyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-3-Ethyl-2,3,4,7-tetrahydro-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-3-ethyl-2,3,4,7-tetrahydro-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-2,3,4,7-Tetrahydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2-Chloro-2,2-difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(3*R*)-4-(2,2-Difluoroethyl)-2,3,4,7-tetrahydro-3-isopropyl-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(7a*R*,10a*S*)-7-Ethyl-7,7a,8,9,10,10a-hexahydro-1-(trifluoromethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

(7a*R*,10a*S*)-7,7a,8,9,10,10a-Hexahydro-1-(trifluoromethyl)-7-(2,2,2-trifluoroethyl)-4*H*-cyclopenta[5,6][1,4]oxazino[2,3-*f*]quinolin-3-one;

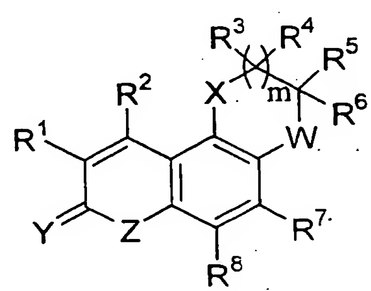
(±)-(2*S*,3*R*)-2,3,4,7-Tetrahydro-2,3-dimethyl-4-(2,2,2-trifluoroethyl)-10-(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(±)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

(–)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one;

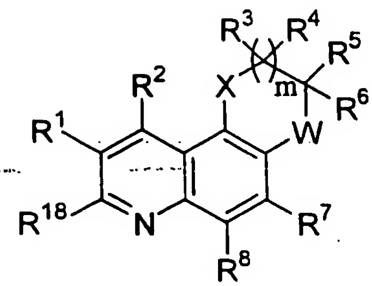
(+)-2,3,4,7-Tetrahydro-4-(2,2,2-trifluoroethyl)-3,10-bis(trifluoromethyl)-8*H*-[1,4]oxazino[2,3-*f*]quinolin-8-one.

58. (currently amended) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of formula:



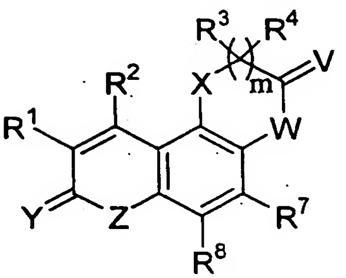
(I)

or



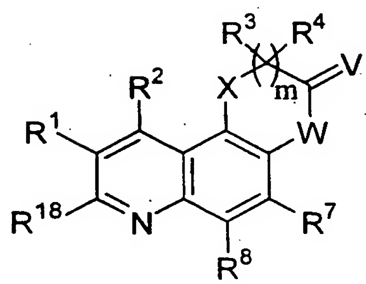
(II)

or



(III)

or



(IV)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally

substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~;

R^3 and R^4 each independently is selected from the group of hydrogen, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~; or

R^3 and R^4 taken together form a three to eight membered saturated or unsaturated carbocyclic or heterocyclic ring; or

R^3 and R^5 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^3 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^5 and R^6 each independently are selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_8$ alkynyl and optionally substituted $C_2 - C_8$ alkenyl~~, wherein the~~

~~alkyl, haloalkyl, heteroalkyl, cycloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~; or

R^5 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring; or

R^5 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring; or

R^6 and R^{13} taken together form a three to eight membered saturated or unsaturated heterocyclic ring;

R^7 is selected from the group of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted~~;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, OR^9, $S(O)_nR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl and heteroaryl groups may be optionally substituted~~;

R^9 is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally substituted arylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted~~;

R^{10} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl, CO_2R^{12}, $C(O)R^{12}$, SO_2R^{12} and $S(O)R^{12}$~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted~~;

R^{11} and R^{12} each independently is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl and optionally

substituted arylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted~~;

R^{13} is selected from the group of optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~;

R^{16} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{12}R^{17}$~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{17} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl and optionally substituted $C_1 - C_8$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{18} is selected from the group of hydrogen, F, Br, Cl, I, CN, $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, ~~$C_1 - C_8$ heteroalkyl~~, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, ~~COR^{17},~~ CO_2R^{17}, $CONR^{16}R^{17}$, SOR^{17} and SO_2R^{17}~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~;

R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_8$ alkyl, optionally substituted $C_1 - C_8$ haloalkyl, optionally substituted $C_1 - C_8$ heteroalkyl, optionally substituted $C_2 - C_8$ alkenyl, optionally substituted $C_2 - C_8$ alkynyl, optionally substituted $C_3 - C_8$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted heteroarylalkyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~;

m is selected from the group of 0, 1 and 2;

n is selected from the group of 0, 1 and 2;

V is selected from the group of O and S;

W is selected from the group of O, $S(O)_n$, NH, $N\{R^{13}\}$, $N\{C(Y)R^{11}\}$ and $N\{SO_2R^{11}\}$;

X and Z each independently is selected from the group of O, $S(O)_n$, NH, $N\{R^{11}\}$, $N\{C(Y)R^{11}\}$, $N\{SO_2R^{12}\}$ and $N\{S(O)R^{12}\}$; and

Y is selected from the group of O, S, $N\{R^{19}\}$ and $N\{OR^{19}\}$;

and pharmaceutically acceptable salts thereof.

59. (original) A pharmaceutical composition according to claim 58, wherein said composition is suitable for enteral, parenteral, suppository or topical administration.

60. (currently amended) A pharmaceutical composition according to claim 58, wherein R^1 is selected from the group of hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_nR^9$, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

61. (currently amended) A pharmaceutical composition comprising a compound according to claim 1, wherein R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_nR^9$, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

62. (currently amended) A pharmaceutical composition according to claim 59, wherein

R^1 is selected from the group of hydrogen, F and optionally substituted $C_1 - C_4$ alkyl;

and

R^2 is selected from the group of hydrogen, optionally substituted $C_1 - C_2$ alkyl, optionally substituted $C_1 - C_2$ haloalkyl and optionally substituted $C_1 - C_2$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

63. (currently amended) A pharmaceutical composition according to claim 58, wherein R^3 is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, $C(Y)OR^{11}$ and $C(Y)NR^{10}R^{11}$~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~; or

R^3 and R^6 taken together form a three to eight membered saturated or unsaturated carbocyclic ring.

64. (currently amended) A pharmaceutical composition according to claim 58, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl and alkenyl groups may be optionally substituted~~.

65. (currently amended) A pharmaceutical composition according to claim 64, wherein R^6 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl, optionally substituted $C_1 - C_4$ heteroalkyl, optionally substituted $C_2 - C_4$ alkynyl and optionally substituted $C_2 - C_4$ alkenyl~~, wherein the alkyl, heteroalkyl, haloalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

66. (currently amended) A pharmaceutical composition according to claim 58, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkynyl and optionally substituted $C_2 - C_6$ alkenyl~~, wherein the alkyl, haloalkyl, heteroalkyl, alkynyl and alkenyl groups may be optionally substituted~~.

67. (currently amended) A pharmaceutical composition according to claim 66, wherein R^5 is selected from the group of hydrogen, CF_3, CF_2Cl, CF_2H, CFH_2, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

68. (currently amended) A pharmaceutical composition according to claim 58, wherein R^7 and R^8 each independently is selected from the group of hydrogen, F, Cl, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

69. (currently amended) A pharmaceutical composition according to claim 58, wherein

R^9 is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, and optionally substituted $C_1 - C_6$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted;~~ and

R^{10} is selected from the group of hydrogen, $S(O)R^{12}$, SO_2R^{12}, $C(O)R^{12}$, CO_2R^{12}, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl and optionally substituted $C_1 - C_6$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

70. (currently amended) A pharmaceutical composition according to claim 58, wherein R^4 is selected from the group of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

71. (currently amended) A pharmaceutical composition according to claim 58, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, optionally substituted $C_1 - C_6$ alkyl, optionally substituted $C_1 - C_6$ haloalkyl, optionally substituted $C_1 - C_6$ heteroalkyl, optionally substituted $C_2 - C_6$ alkenyl, optionally substituted $C_2 - C_6$ alkynyl, optionally substituted $C_3 - C_6$ cycloalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted arylalkyl and optionally substituted ~~heteroarylalkyl, wherein the alkyl, haloalkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl and heteroarylalkyl groups may be optionally substituted~~; or

R^6 and R^{13} taken together form a five to seven membered saturated or unsaturated heterocyclic ring.

72. (currently amended) A pharmaceutical composition according to claim 71, wherein R^{13} is selected from the group of CF_3, CF_2Cl, CF_2H, CFH_2, CH_2CF_3, CH_2CF_2Cl, CH_2CCl_2F, methyl, ethyl, propyl, isopropyl, isobutyl, cyclopropylmethyl, and allyl; or

R^6 and R^{13} taken together form a five membered saturated or unsaturated heterocyclic ring.

73. (currently amended) A pharmaceutical composition according to claim 58, wherein R^{18} is selected from the group of hydrogen, F, Cl, OR^{16}, SR^{16}, $NR^{16}R^{17}$, $C_1 - C_4$

alkyl, and optionally substituted $C_1 - C_4$ ~~haloalkyl and $C_1 - C_4$ heteroalkyl, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

74. (currently amended) A pharmaceutical composition according to claim 58, wherein R^{19} is selected from the group of hydrogen, optionally substituted $C_1 - C_4$ alkyl, optionally substituted $C_1 - C_4$ haloalkyl and optionally substituted $C_1 - C_4$ heteroalkyl~~, wherein the alkyl, haloalkyl and heteroalkyl groups may be optionally substituted~~.

75. (original) A pharmaceutical composition according to claim 58, wherein m is 0 or 1.

76. (original) A pharmaceutical composition according to claim 58, wherein

W is selected from the group of NH, N{R^{13}}, N{C(Y)R^{11}} and N{SO_2R^{11}}; and

X is selected from the group of O, S, NH and N{R^{11}}.

77. (original) A pharmaceutical composition according to claim 58, wherein

Y is O or S; and

Z is selected from the group of NH, N{R^{11}} and O.

78. (canceled)

79. (canceled)

80. (currently amended) A method ~~of~~ for treating an individual having a condition mediated by an androgen receptor comprising administering to said individual a pharmaceutically effective amount of a compound according to any one of claims 1, 56, or 57.

81. (currently amended) ~~A~~ The method according to claim 80, wherein said compound is represented by formula (I).

82. (currently amended) ~~A~~ The method according to claim 80, wherein said compound is represented by formula (II).

83. (currently amended) ~~A~~ The method according to claim 80, wherein said compound is represented by formula (III).

84. (currently amended) ~~A~~ The method according to claim 80, wherein said compound is represented by formula (IV).

85. (currently amended) ~~A~~ The method according to claim 80, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction,

impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, and hormone-dependent cancers.

86. (currently amended) ~~A~~ The method according to claim 80, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

87. (currently amended) A method ~~of~~ for modulating an androgen receptor in an individual comprising administering to said individual an androgen receptor modulating effective amount of a compound according to any one of claims 1, 56, or 57.

88. (currently amended) ~~A~~ The method according to claim 87, wherein said individual has a condition mediated by an androgen receptor.

89. (original) A method according to claim 87, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

90. (currently amended) ~~A~~ The method according to claim 87, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

91. (currently amended) ~~A~~ The method according to claim 87, wherein said modulation is activation.

92. (currently amended) ~~A~~ The method according to claim 91, wherein said individual has a condition mediated by an androgen receptor.

93. (currently amended) ~~A~~ The method according to claim 92, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

94. (currently amended) ~~A~~ The method according to claim 92, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

95. (currently amended) ~~A~~ The method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 100 nM.

96. (currently amended) ~~A~~ The method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 50 nM.

97. (currently amended) ~~A~~ The method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 20 nM.

98. (currently amended) ~~A~~ The method according to claim 91, wherein said compound provides 50% maximal activation of AR at a drug concentration of less than 10 nM.

99. (currently amended) ~~A~~ The method according to claim 87, wherein said modulation is inhibition.

100. (currently amended) ~~A~~ The method according to claim 99, wherein said individual has a condition mediated by an androgen receptor.

101. (currently amended) ~~A~~ The method according to claim 100, wherein said condition is selected from the group of acne, male-pattern baldness, sexual dysfunction, impotence, wasting diseases, hirsutism, hypogonadism, prostatic hyperplasia, osteoporosis, cancer cachexia, hormone-dependent cancers and a process mediated by an anabolic agent.

~~101~~102. (currently amended) ~~A~~ The method according to claim 100, wherein said condition is alleviated with a therapy selected from the group of male hormone replacement therapy, female androgen replacement therapy and stimulation of hematopoiesis.

103. (currently amended) ~~A~~ The method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 100 nM.

104. (currently amended) ~~A~~ The method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 50 nM.

105. (currently amended) The ~~A~~ method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 20 nM.

106. (currently amended) ~~A~~ The method according to claim 99, wherein said compound provides 50% maximal inhibition of AR at a drug concentration of less than 10 nM.

107. (currently amended) A method ~~of~~ for treating cancer, comprising administering to a patient in need thereof a pharmaceutically effective amount of a compound according to any one of claims 1, 56 or 57.

REMARKS

This Amendment and Response is submitted in response to the Office Action mailed July 29, 2004 (Office Action). A supplemental Information Disclosure statement (IDS) accompanies this response. A check for $1200 for the fee for a three-month extension of time ($1020) and for the fee for filling the supplemental IDS ($180) accompanies this response. Any fees that may be due in connection with the filing of this paper or with this application may be charged to Deposit Account No. 06-1050. If a Petition for Extension of Time is needed, this paper is to be considered such Petition.

Claims 1-77 and 80-107 are pending. Claims 78 and 79 are cancelled herein without prejudice or disclaimer. Claims 1-3, 5-7, 9, 11-18, 20-21, 23, 25, 27, 29-30, 32, 35, 49-50, 58, 60-74, 80-88, and 90-107 are amended herein clarity. Support for amendments is found throughout the specification and, in particular, in the respective claims as originally filed. Claim 1 is amended to include the recitation –a modulator for a member of the androgen receptor family–, basis for which is found throughout the specification (for example, see page 45, lines 19-20). Claims 1, 32, and 50 have also been amended to remove certain substituents from R^{18}. Support these amended claims is found throughout the specification, for example at page 16, lines 7-10 and page 26 and in the claims as originally filed. Therefore, no new matter has been added by reason of these amendments.

Informalities

A. Incorporation By Reference

The Examiner objects to incorporation by reference of certain material in the specification. Office Action at page 2. Specifically, the Examiner alleges that references at page 110, line 22 and at page 111, lines 25-26 describing the "co-transfection assay" constitute essential material. This rejection is respectfully traversed.

Incorporation by reference of "essential material" and "nonessential material" is discussed in the MPEP at MPEP § 608.01(p)(I). For example, MPEP § 608.01(p)(I)(A) states:

> "Essential material" is defined as that which is "necessary to (1) describe the claimed invention, (2) provide an enabling disclosure of the claimed invention, or (3) describe the best mode (35 U.S.C. 112)" …
>
> Nonessential subject matter is subject matter referred to for purposes of indicating the background of the invention or illustrating the state of the art.

MPEP § 608.01(p)(I) also states that

> Nonessential subject matter may be incorporated by reference to (1) patents or applications published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications, or (3) non-patent publictions….

The references objected to by the Examiner are Evans *et al*. on page 110, line 22, US Pat. Nos. 4,981,784 and 5,071,773 to Evans *et al*. on page 110, lines 25-26 and Berger *et al*. on page 111, lines 8-9. These references describe a co-transfection assay that mimics an *in vivo* system in the laboratory. One of skill in the art will recognize that the assay described in the references can be used to in assessing certain compounds, but is not subject matter claimed in the application.

The references illustrate the state of the art at the time of filing the original application with respect to assays available for assessing *in vivo* pharmacology of various compounds, including the claimed subject matter. For example, Evans *et al*. (U.S. Pat. No. 5,071,773) teaches that its bioassays are useful for evaluating whether compounds are functional ligands for receptor proteins (see claim 2 and Abstract). The ability of a compound or composition to modulate the transcriptional ability of intracellular receptors including RXRs may be measured by any of the assays known to those of skill in the art, including but not limited to the co-transfection (cis-trans) assays. Such assays are described in, e.g., U.S. Pat. Nos. 4,981,784, 5,071,773, 5,298,429, 5,506,102, as well as in WO89/05355, WO91/06677, WO92/05447, WO93/11235, WO93/23431, WO94/23068, WO95/18380 and CA 2,034,220. Heyman *et al*. (Cell, 68:397-406 (1992)) also teaches such assays. Thus, because the references cited by the Examiner as allegedly being incorrectly incorporated by reference illustrate the state of the art, the references are nonessential material, and are properly incorporated by reference under MPEP § 608.01(p)(I).

Even without the incorporated references, the application describes the assay with sufficient detail to allow one of skill in the art to practice the assay. The Examiner's attention is directed to the *Biological Examples* section of the application on page 110, line 20 through page 114, line 5. For example, Example B of the *Biological Examples* section, page 112, line through page 114, line, entitled *Co-transfection assay*, provides a detailed description of the assay. The references clearly illustrate that one of skill in the art could use such assays to assess the claimed compounds.

The Examiner cites to *In re Hawkins* to support the objection that the above-noted references are improperly incorporated by reference in the application. This is inapt. In *In re Hawkins*, the incorporated material is deemed essential subject matter. The incorporated material described how to make starting materials, which the Board found were necessary to make the claimed compounds. See *In re Hawkins*, 179 U.S.P.Q. 157, 165. As discussed above, the references illustrate the state of the art at the time of filing the application. Hence,

the references are nonessential material and are properly incorporated by reference. Applicant respectfully requests that the objection be withdrawn.

B. Typographical Errors

The Examiner notes that a typographical error appears on page 83 of the specification. Applicant has corrected the error by the amendment of the specification herein.

The Examiner notes that claim 102 was incorrectly numbered "101" and indicates that the second claim numbered "101" has been renumbered as "102" under 37 C.F.R. § 1.126. Applicant has corrected the error and will use the correct designation in all subsequent submissions.

THE REJECTION OF CLAIMS 1-55 AND 58-107 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1-55 and 58-107 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being broader than the enabling disclosure because it alledgely would require undue experimentation to make and use all of the compounds within the scope of the claims. The Examiner relies on the factors set forth in *In re Wands* to reach this conclusion. This rejection is respectfully traversed.

RELEVANT LAW

The test of enablement is whether one skilled in the art can make and use what is claimed based upon the disclosure in the application and information known to those of skill in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). A certain amount of experimentation is permissible as long as it is not undue. A patent application need not teach, and preferably omits, what is well known in the art. *Spectra-Physics, Inc. v. Coherent, Inc.*, 3 USPQ2d 1737 (Fed. Cir. 1987). Indeed, "not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted." *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332. Showing every combination of substituents is unnecessary.

A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *See, Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

ANALYSIS

Applying the above-noted factors to the instant facts reveals that the amount of experimentation is not undue.

1. The scope of the claims.

Claim 1 is directed to a compound having the formula of I, II, III or IV, and claims 2-57 ultimately depend from claim 1 and are directed to various embodiments thereof. Claim 58 is directed to a pharmaceutical composition including a pharmaceutically acceptable carrier and a compound of formula I, II, III or IV, and claims 59-77 ultimately depend from claim 58 and are directed to various embodiments thereof. Claim 80 is directed to a method of treating an individual having a condition mediated by an androgen receptor that includes administering to the individual a pharmaceutically effective amount of a compound of any one of claims 1, 56, or 57. Claims 81-86 depend from claim 80 and are directed to various embodiments thereof. Claim 87 is directed to a method of modulating an androgen receptor in an individual that includes administering to the individual an androgen receptor modulating effective amount of a compound of any one of claims 1, 56, or 57. Claims 88-106 ultimately depend from claim 87 and are directed to various embodiments thereof. Claim 107 is directed to a method of treating cancer that includes administering to a patient in need thereof a pharmaceutically effective amount of a compound of any one of claims 1, 56 or 57.

2. Level of skill in the art

As the Examiner noted, the skill in the art of chemical synthesis is high. That skill, together with the instant specification, including cited and incorporated references, allow the skilled artisan to make any and all of the claimed compounds. The Examiner went on to note that "the level of skill in the medicinal arts is moderate because it is unclear which if any of the compounds disclosed herein are active against one or more specific disease conditions." Office Action at page 5. Applicant respectfully disagrees. The level of skill in the medical arts is high. This is evidenced by the art in this area, which is authored primarily by those with Ph.D. and M.D. degrees and is intended for an audience of similarly highly skilled individuals, primarily in the fields of biochemical, pharmaceutical, or medical arts. The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, address a highly skilled audience, and further evidence the high level of skill in this art. Therefore, the amount of disclosure required to meet the enablement requirement is minimal.

3. The amount of direction or guidance presented and the presence or absence of working examples.

The specification provides a general description of non-steroidal compounds that are high-affinity, high-specificity agonists, partial agonists (i.e., partial activators and/or tissue-specific activators) and antagonists for androgen receptors (AR). The claimed subject matter is directed to androgen receptor modulator compounds, pharmaceutical compositions containing such compounds as well as methods of using such compounds and pharmaceutical compositions for modulating processes mediated by steroid receptors. The application discloses methods of making such compounds and pharmaceutical compositions, as well as intermediates used in their synthesis. The specification describes seven generic synthesis schemes (for example, see page 33, 35, 37, 38, 39, 41 and 42). One of skill in the art can readily follow these schemes or known variations of such schemes with any of a vast number of commonly available starting materials to arrive at the claimed subject matter. The application names over 150 exemplary AR modulator compounds (for example, see page 29 through 32 and claims 56 and 57.

The specification also provides over 50 working examples. Hence the specification provides a variety of examples of compounds that fall within the scope of the claims evidencing that the claimed compounds function as claimed. The specification also provides two screening assays. As discussed above, various screening assays for assessing the ability of a compound or composition to modulate the transcriptional ability of intracellular receptors are known to those of skill in the art, such as those described in U.S. Pat. Nos. 4,981,784, 5,071,773, 5,298,429, and 5,506,102 and in WO89/05355, WO91/06677, WO92/05447, WO93/11235, WO93/23431, WO94/23068, WO95/18380 and CA 2,034,220. The requirements of 35 U.S.C. §112, first paragraph, do not require a specific example of everything within the scope of the claims. *In re Anderson*, 176 USPQ 331, 333 (CCPA 1973) :

> ...we do not regard section 112, first paragraph, as requiring a specific example of everything within the scope of a broad claim . . . What the Patent Office is here apparently attempting is to limit all claims to the specific examples, not withstanding the disclosure of a broader invention. This it may not do.

In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960) :

> It is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species. It is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it.

Hence there is no requirement for the applicant to exemplify or even provide an example of everything within the scope of the claims. The Patent Office cannot "limit all claims to the specific examples, notwithstanding the disclosure of a broader invention."

4. Predictability of the art.

The art of chemical synthesis is predictable and is dictated by recognized chemical reactions and constraints. The medical arts are also predictable, in that various assays and models that mimic an *in vivo* system in the laboratory were available and known to the skilled artisan at the time of filing of the application. For example, see U.S. Pat. No. 5,071,773 to Evans *et al.* (1991), which teaches a bioassay for evaluating whether compounds are functional ligands for receptor proteins. Such assays are routine in the medical arts. Thus, it is not necessary that one skilled in the art be able to predict which compound will be most active for a particular medical application. The specification, in view of the skill in the art, describes how to make and administer, and if necessary test, any claimed compound. As discussed above, the level of knowledge and skill in the preparation, isolation, manipulation and compounds was high as of the filing date of the instant application. Therefore, in view of the teachings of the specification, in combination with what was known at the time the original application was filed, applicant respectfully submits that the claimed compounds can be prepared predictably using any methods that are known to those skilled in this art. Further, formulating such compounds into a pharmaceutical composition and administration of such compositions to a subject is well know in the medical arts. Thus, preparation and administration of pharmaceutical compounds is also predictable.

5. The amount of experimentation required.

There is nothing of record to suggest that production or use of any of the claimed compounds or compositions would require development of new procedures or excessive experimentation. Organic synthesis methods have been used for decades. As discussed above, bioassays for evaluating whether compounds are functional ligands for receptor proteins were known in the art since at least 1991. Such assays are routine in this art and do not require excessive experimentation. It is noted that the test for undue experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . ." *In re Wands* 858 F.3d 731, 737 (Fed Cir. 1988). Thus, methods for making and evaluating androgen receptor modulator compounds were available and known to skilled artisans at the time of filing the application. Those skills, together with the teaching of the specification, including cited and incorporated references, allow the skilled artisan to

make any and all of the claimed compounds. As discussed, it is not necessary that one skilled in the art be able to predict which compound will be most active for a particular medical application. The specification, in view of the skill in the art, enables one to make and administer, and if necessary test, any claimed compound

CONCLUSION

In light of the scope of the claims, the teachings in the specification, the high level of skill of those in this art, the working examples, and the extensive knowledge of those of skill in this art, it would not require undue experimentation for a person skilled in the art to make and use the claimed compounds and compositions. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter. Applicant respectfully requests that the rejection be reconsidered and withdrawn.

Policy Considerations

The Examiner is reminded that applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed. Moreover, it is unfair, unduly limiting and contrary to the public policy and constitutional mandate that underlie the U.S. patent system to require applicant to limit the instant claims to the compounds specifically discussed in the examples. To do so permits one of skill in this art to practice the disclosed invention but avoid liability for infringement merely by selecting a species of the disclosed genus not specifically discussed in the examples.

As a broad body of knowledge is available in the area of chemical, it would be unfair, unduly limiting and contrary to the public policy upon which the patent laws are based to require Applicant to limit these claims to the particular exemplary embodiments. See, e.g., *In re Goffe*, 542 F.2d 801, 166 USPQ 85 (CCPA 1970):

> for the Board to limit appellant to claims involving the specific materials disclosed in the examples so that a competitor seeking to avoid infringing the claims can merely follow the disclosure and make routine substitutions "is contrary to the purpose for which the patent system exists - to promote progress in the useful arts".
>
> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions. *In re Sus and Schafer*, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

To require applicant to further limit the claims would permit those of skill in the art to practice what is disclosed in the specification but avoid infringing claims so-limited. To permit

that is simply not fair. The instant application in light of the knowledge of those of skill in the art provides adequate guidance for making and using androgen receptor modulator compounds and compositions. Having done so, it is now routine for others to make minor modifications by any method known in this art. Those of skill in the art should not be permitted to make minor modifications, such as selecting a compound not specifically disclosed in the examples, to avoid infringing such claims.

Rebuttal to Examiner's Arguments

A. Alleged Excessive Breadth of Claims

The Examiner alleges that the "breadth of the compound claims is excessive," asserting that "the term 'may be optionally substituted' without specifying the substituents implied thereby renders the breadth excessive because said term implies that the unnamed substituents is/are open to all possible alternatives" (Office Action at page 4). Applicant respectfully points out that the term "optionally substituted" is defined in the specification at page 11 line 26 to page 12, line 9, which states:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

Thus, the claims are not unbound as the Examiner asserts. Applicant respectfully requests that the Examiner reconsider the rejection in view of the above.

B. Nature of the Invention

The Examiner alleges that the "nature of the invention includes a method of testing, a method of purification, and a vast number of methods of medicinal treatment" (Office Action at page 4). Applicant respectfully submits that it does not constitute undue experimentation to make, test, and administer any compound of the invention. It is not necessary that one skilled in the art be able to predict precisely which compounds will be the most active for a given disease, because testing compounds in a screening assay, such as the binding assay or the co-transfection assay, both of which are described in the specification, does not constitute undue

experimentation. Indeed, synthesizing and testing compounds is analogous to the process of making and screening antibodies, which the Federal Circuit found not to be undue experimentation. *In re Wands* 858 F.3d 731, 8 U.S.P.Q.2d 1400.

C. Specific Disease Conditions

The Examiner alleges that there is no clear showing that compounds that are active as androgen receptor modulators (agonists or antagonists) are actually effective in the treatment of any specific disease condition Office Action page 5). The Examiner requests copies of any art bearing on this topic.

Applicant respectfully submits that at the time of filing the application, use of androgen receptor modulators, such as agonists or antagonists, as therapeutic agents was known to those skilled in the medical arts. For example, Singh *et al.* (*Current Medicinal Chemistry* (2000) **7**: 211-247) teaches that benign prostatic hyberplasia, acne, seborrhea, hirsutism and androgenic alopecia are all well recognized to be sensitive to androgens and to respond to androgen receptor antagonist therapy (page 211, first paragraph). Boyer (*Australian Prescriber* (1996) **19**: 22-24) teaches that steroidal and non-steroidal antiandrogens are used in the hormonal management of prostate cancer amd as part of total androgen blockade. Claman *et al.* (*J Obstet Gynaecol Can* (January 2002) **24**(1): 62-67) teaches androgen suppression and/or androgen recptor blockade for medical treatment of hirsutism and the associated diseases hyperandrogenism and adult-onset congenital adrenal hyperplasia. Copies of these articles are supplied herewith. Thus, there is a clear showing in the art that compounds that are active as androgen receptor modulators are actually effective in the treatment of *many* specific disease conditions.

D. Alleged Limited Direction

The Examiner states that the amount of direction provided is limited to the chemical synthesis of numerous [1,4]oxazino[2,3-*f*]quinolin-8-ones and data identifying which compounds are agonists or antagonists and alleges that no other chemical species has been disclosed as having been synthesized, isolated or subjected to any testing to determine possible medicinal activity. Applicant respectfully disagrees.

The specification teaches seven generic synthesis schemes (for example, see page 33, 35, 37, 38, 39, 41 and 42). The application names over 150 exemplary AR modulator compounds (for example, see page 29 through 32 and claims 56 and 57). The specification also provides over 50 working examples and two screening assays. It is respectfully submitted that the direction provided by the specification is sufficient to allow one of skill in the art to synthesize, test and administer any and all compounds of the claimed subject matter. One

skilled in the art will recognize that the generic schemes may be used to synthesize such compounds, though they may also be synthesized using techniques known to those of skill in the art. Similarly, one of skill in the art may assess certain compounds of the present invention using the binding assay or the co-transfection assay, both of which are disclosed in the specification, though one of skill in the art may assess compounds using other known assays. Finally, administration of compounds is routine to one of skill in the medical arts.

E. Alleged Lack of a Showing of Efficacy of Treatment of a Specific Disease

The Examiner alleges that the specification provides biological testing limited to the compounds noted in the Examples and that the testing was limited "to showings of agonist or antagonist activity in the presence of a receptor, but no showing of efficacy in the treatment of any one of the specific disease conditions listed" (Office Action page 5). The Examiner also states that applicant has shown that the dislcosed compounds have potential utility in the treatment of diease conditions where an androgen-sensitive receptor is implicated but contends that there has been no showing that any particualr disease may be effectively treated using any claimed compound (Office Action pages 5-6).

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for an area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, method; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of skill in the art how to make and use the claimed subject matter without undue experimentation. The teachings of Evans *et al.* (US Pat. Nos. 4,981,784 and 5,071,773 and *Science* **240**:889-95 (1988)) describe a co-transfection assay that mimics an *in vivo* system in the laboratory. Elbrecht *et al.* (U.S Pat. No. 5,872,150) discloses assays for identifying compounds with antiandrogenic activity employing a hamster ductus deferens cell line. Raynaud *et al.*(*J. Steroid Biochem.* **12**:143-157 (1980)) describes a number of steroid hormone receptor competition assays. Tanabe *et al.* (U.S. Pat. No. 5,723,455) descibes a rat prostate androgen receptor competition assay for *in vitro* evaluation of androgen receptor modulator compounds. These references support the teachings of the specification and demonstrate the knowlegde of those of skill in the art at the time the application was filed. These references also provide evidence that those of skill in this art correlate activity in the assays with pharmacological activity. Furthermore,

compounds that have shown activity in these assays (see, *e.g.*, U.S. Patent No. 6,043,279) have shown activity in clinical trials and are now recognized therapeutics.

One of skill in the art would recognize that the assays described in the references and the specification are useful in assessing certain compounds including those presently claimed in the treatment of disease conditions where an androgen-sensitive receptor has been implicated. As discussed above, a number of diseases, including benign prostatic hyberplasia, prostate cancer, acne, seborrhea, hirsutism, hyperandrogenism, adult-onset congenital adrenal hyperplasia and androgenic alopecia, are recognized to be sensitive to androgens and to respond to androgen receptor antagonist therapy. Therefore, compounds that are androgen receptor antagonists, for example, are candidates for clinical use in the treatment of diseases that respond to androgen receptor antagonist therapy.

REJECTION OF CLAIMS 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 AND 86-107 UNDER 35 U.S.C. § 112 SECOND PARAGRAPH

Claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77 and 86-107 under 35 U.S.C. § 112 second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter. This rejection is respectfully traversed.

RELEVANT LAW

Claims are not read in a vacuum but instead are considered in light of the specification and the general understanding of the skilled artisan. *Rosemount Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1547, 221 USPQ 1, 7 (Fed. Cir. 1984), *Caterpillar Tractor Co. v. Berco, S.P.A.*, 714 F.2d 1110, 1116, 219 USPQ 185, 188 (Fed. Cir. 1983). A claim is not indefinite when one skilled in the art would understand the language in the claims when read in light of the specification.

35 U.S.C. § 112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. Claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. *Shatterproof Glass Corp. v. Libby-Owens Ford Col.*, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir.), cert. dismissed, 106 S.Ct. 340 (1985).

A. Alleged Incomplete Recitation

The Examiner rejects claims 1-7, 9, 11-18, 20, 21, 23-36, 39, 41, 45, 49-51, 56-58, 60-74, 76, 77, 85, 86, 89, 90, 93, 94, 101 and 102 because the recitation "selected from the group of" allegedly is incomplete because the Examiner urges that Markush groups are

properly formatted using the phrase "selected from the group <u>consisting</u> of" (Office Action at page 6). While use of the term "comprising" instead of "consisting" is not allowed, alternative wording is permitted. MPEP 2173.05(h) (noting that Markush group claims "may be recited in the traditional manner, or alternatively."). The recitation "selected from the group of" reasonably apprises those of skill in the art of the bounds of the claimed subject matter. Hence, the claim language is acceptable. Further, the phrase "selected from the group of" is closed to additional members and, thus, permitted.

B. "Optionally Substituted"

Claims 1-7, 9, 11-18, 20, 21-25, 27-29, 30, 32, 35, 36, 49, 50, 58, 60-62, 64-71, 73 and 74 are rejected because the recitation "may be optionally substituted" is allegedly incomplete because it allegedly fails "to specify the substituents implied thereby." Office Action at pages 6-7. This rejection is respectfully traversed..

As noted above, the term "optionally substituted" is defined in the specification at page 11, line 26 to page 12, line 9, which recites:

> "Optionally substituted" groups may be substituted or unsubstituted. The substituents of an "optionally substituted" group may include, without limitation, one or more substituents independently selected from the following groups or designated subsets thereof: alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, haloalkenyl, haloalkynyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkoxy, aryloxy, haloalkoxy, amino, alkylamino, dialkylamino, alkylthio, arylthio, heteroarylthio, oxo, carboxyesters, carboxamido, acyloxy, hydrogen, F, Cl, Br, I, CN, NO_2, NH_2, N_3, $NHCH_3$, $N(CH_3)_2$, SH, SCH_3, OH, OCH_3, OCF_3, CH_3, CF_3, $C(O)CH_3$, CO_2CH_3, CO_2H, $C(O)NH_2$, OR^9, SR^9 and $NR^{10}R^{11}$. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., $-CH_2CH_2F$) or substituted at a level anywhere in-between fully substituted and monosubstututed (e.g., $-CH_2CF_3$).

It is respectfully submitted that one skilled in the art would understand the language in the claims when read in light of the specification. As shown above, the meaning of the recitation "optionally substituted" reasonably apprises those of skill in the art of the bounds of the claimed subject matter. Applicant respectfully requests that the Examiner reconsider the rejection in view of the above.

C. Inadvertant Omission

Claim 61 is rejected because of the inadvertent omission of the term "comprising a compound." Applicant thanks the Examiner for pointing out this error, which is corrected herein. Thus, the rejection is now moot.

D. Claims 87-107

Claims 87-107 are rejected because the Examiner alleges that the term "modulate" is "indefinite for failing to indicate what specific treatment action(s) or effect(s) is(are) intended." It is respectfully submitted that the specification specifically states that "in one aspect, the modulation is activation, while in another aspect, the modulation is inhibition" (see, for example, page 17, lines 4-5). This is in keeping with the use of the term "modulators" throughout the specification, which refer to "compounds that are agonists, partial agonists or antagonists" (see page 1, lines 25-26), where "a compound that binds an IR [intracellular receptor] and mimics the effect of the native ligand is referred to as an "agonist", while a compound that inhibits the effect of the native ligand is called an "antagonist." Thus, when read in light of the specification, one skilled in the art would understand the meaning of the term "modulate" in the claims.

REJECTIONS UNDER 35 U.S.C. § 102

Claims 1-7, 9, 11-14, 16-22, 27, 28, 37, 41, 42, 53, 58-62, 64, 66-68, 73, 75, 80, 82 and 85-107 are rejected as allegedly anticipated by U.S. Pat. Nos. 6,030,967 and 6,340,704 to Marui *et al.* Without acquiescing to the Examiner's allegation and solely to expedite prosecution, claims 1, 32, and 50 are amended herein. Amended claims 1, 32, and 50 are not anticipated by the two Marui *et al.* patents. The remaining rejected claims ultimately depend from those claims. Thus, the rejections under 35 U.S. C. § 102 are moot.

* * *

In view of the above, reconsideration and allowance is respectfully requested.

Respectfully submitted,

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 18202-018001 (1082)
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.	: 20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 3 – copies of the letter sent to inventor Thompson [the letter was accompanied by copies of the original specification, amendments made during prosecution and the substitute DECLARATION, copies of which are provided in EXHIBIT 2]

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October 30, 2006

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Anthony Thompson
4179 Third Avenue, Apt. 211
San Diego, CA 92103

Re: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Applicant:	**Lin Zhi *et al.***
Application No.:	**10/080,503**
Filing Date:	**February 22, 2002**
Country:	**United States**
Your Ref.:	**016-0082.A.US**
Our Ref.:	**18202-018001/1082**

Dear Mr. Thompson:

Enclosed is a Declaration for Patent Application for your execution. The above-captioned patent application was prepared and filed with the U.S. Patent and Trademark Office on February 22, 2002. This patent application has been deemed allowable. The Examiner has required a replacement Declaration because the hand-annotated address changes made by one of the inventors was not initialed on the originally submitted Declaration.

We also have enclosed a copy of the application as filed with the U.S. Patent and Trademark Office for your review. Also enclosed are copies of the Amendments that have been filed during prosecution of this patent application. Please review the application and the amendments.

After reviewing the application and the amendments, please sign and date the enclosed Declaration for Patent Application and return the executed document to our office as soon as possible. For your convenience we have enclosed a stamped, self-addressed envelope for use in returning the executed document to us.

In the event that the enclosed Declaration for Patent Application is incorrect in anyway, please mark through the error(s), type or print the correction(s) above it, and then ***initial*** and ***date*** in the margin beside the correction(s).

We would appreciate the prompt execution and return of the enclosed Declaration for Patent Application. If you have any questions, please do not hesitate to contact our office.

Sincerely,

Stephanie Seidman

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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EXHIBIT 4 – copies of the letter sent to inventor Cummings [the letter was accompanied by copies of the original specification, amendments made during prosecution and the substitute DECLARATION, copies of which are provided in EXHIBIT 2]

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1855-1930

W.K. Richardson
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October 30, 2006

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Marquis L. Cummings
917 Bracero Road
Encinitas, CA 92024

Re: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Applicant:	**Lin Zhi *et al.***
Application No.:	**10/080,503**
Filing Date:	**February 22, 2002**
Country:	**United States**
Your Ref.:	**016-0082.A.US**
Our Ref.:	**18202-018001/1082**

Dear Mr. Cummings:

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Sincerely,

Stephanie Seidman

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Sent To Marquis L. Cummings

Street, Apt. No.; or PO Box No. 917 Bracero Rd.

City, State, ZIP+4 Encinitas, CA 92024

PS Form 3800, June 2002 See Reverse for Instructions

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 5 – copies of the letter sent to inventor Edwards [the letter was accompanied by copies of the original specification, amendments made during prosecution and the substitute DECLARATION, copies of which are provided in EXHIBIT 2]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
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FISH & RICHARDSON P.C.

12390 El Camino Real
San Diego, California
92130

Telephone
858 678-5070

Facsimile
202 626-7796

Web Site
www.fr.com

Stephanie Seidman
(858) 678-4777

Email
seidman@fr.com

October 30, 2006

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

James P. Edwards
8723 Hesby Court
San Diego, CA 92129

Re: TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

Applicant:	**Lin Zhi *et al.***
Application No.:	**10/080,503**
Filing Date:	**February 22, 2002**
Country:	**United States**
Your Ref.:	**016-0082.A.US**
Our Ref.:	**18202-018001/1082**

Dear Mr. Edwards:

Enclosed is a Declaration for Patent Application for your execution. The above-captioned patent application was prepared and filed with the U.S. Patent and Trademark Office on February 22, 2002. This patent application has been deemed allowable. The Examiner has required a replacement Declaration because the hand-annotated address changes made by one of the inventors was not initialed on the originally submitted Declaration.

We also have enclosed a copy of the application as filed with the U.S. Patent and Trademark Office for your review. Also enclosed are copies of the Amendments that have been filed during prosecution of this patent application. Please review the application and the amendments.

After reviewing the application and the amendments, please sign and date the enclosed Declaration for Patent Application and return the executed document to our office as soon as possible. For your convenience we have enclosed a stamped, self-addressed envelope for use in returning the executed document to us.

In the event that the enclosed Declaration for Patent Application is incorrect in anyway, please mark through the error(s), type or print the correction(s) above it, and then ***initial*** and ***date*** in the margin beside the correction(s).

We would appreciate the prompt execution and return of the enclosed Declaration for Patent Application. If you have any questions, please do not hesitate to contact our office.

Sincerely,

Stephanie Seidman

SLS/tes
Enclosures
10678705.doc

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Total Postage & Fees	$

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7005 1820 0006 3811 8600

Sent To: James P. Edwards

Street, Apt. No.; or PO Box No.: 8723 Hesby Court

City, State, ZIP+4: San Diego, CA 92129

PS Form 3800, June 2002 — See Reverse for Instructions

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Lin Zhi *et al.*	Art Unit	: 1623
Serial No.	: 10/080,503	Examiner	: Lawrence E. Crane, Ph.D.
Conf. No.	: 8671	Customer No.:	20985
Filed	: February 22, 2002		
Title	: **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**		

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 6 – copy of the Return Receipt postcard from the package sent to inventor Edwards.

SENDER: *COMPLETE THIS SECTION*

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:

James P. Edwards
8723 Hesby Court
San Diego, CA 92129

2. Article Number (*Transfer from service label*) 7005 1820 0006 3811 8600

COMPLETE THIS SECTION ON DELIVERY

A. Signature
X Jackie Edwards ☐ Agent ☐ Addressee

B. Received by (*Printed Name*) MD32

C. Date of Delivery 10.31.06

D. Is delivery address different from item 1? ☐ Yes
If YES, enter delivery address below: ☐ No

3. Service Type
☒ Certified Mail ☐ Express Mail
☐ Registered ☐ Return Receipt for Merchandise
☐ Insured Mail ☐ C.O.D.

4. Restricted Delivery? (*Extra Fee*) ☐ Yes

PS Form 3811, February 2004 Domestic Return Receipt 102595-02-M-1540

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*		Art Unit : 1623	
Serial No. : 10/080,503		Examiner : Lawrence E. Crane, Ph.D.	
Conf. No. : 8671		Customer No.: 20985	
Filed : February 22, 2002			

Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 7 – copy of the returned original envelope stamped by the USPS from the package sent to inventor Caferro.

PLACE STI[illegible]T TOP OF ENVELOPE TO THE RIGHT OF THE RE[illegible] ADDRESS. FOLD AT DOTTED LINE

CERTIFIED MAIL™

7005 1820 0006 3811 8617

UNITED STATES POSTAGE
PITNEY BOWES
02 1A $ 13.25⁰
0004383970 OCT 30 2006
MAILED FROM ZIP CODE 92122

FISH & RICHARDSON P.C.

12390 El Camino Real
San Diego, California
92130-2081

VTF

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P[illegible]
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UNDELIVERABLE
AS ADDRESSED
AT HOLLY SPRINGS NC 27540

18202-018001/1082

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 8 – copy of the returned original envelope stamped by the USPS from the package sent to inventor Thompson.

PLACE STICKER AT TOP OF ENVELOPE TO THE RIGHT OF THE RETURN ADDRESS, FOLD AT DOTTED LINE

CERTIFIED MAIL™

7005 1820 0006 3811 8594

12

UNITED STATES POSTAGE
PITNEY BOWES
02 1A
$ 09.25⁰
0004383970
OCT 30 2006
MAILED FROM ZIP CODE 92122

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12390 El Camino Real
San Diego, California
92130-2081

RETURN TO SENDER

UNDELIVERABLE AS ADDRESSED
INSUFFICIENT ADDRESS
ATTEMPTED NOT KNOWN
NO SUCH NUMBER
OTHER
ROUTE / INITIALS

NKW
310
8
11-1-6

Anthony Thompson
4179 Third Avenue, Apt. 211
San Diego, CA 92103

18202-018001/1082

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 9 – copy of the Return Receipt postcard from the package sent to inventor Cummings.

SENDER: *COMPLETE THIS SECTION*	*COMPLETE THIS SECTION ON DELIVERY*
■ Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired. ■ Print your name and address on the reverse so that we can return the card to you. ■ Attach this card to the back of the mailpiece, or on the front if space permits.	A. Signature X Reeanna Cummings ☒ Agent ☐ Addressee B. Received by (*Printed Name*) Leeanna Cummings C. Date of Delivery 11-13-06
1. Article Addressed to: Marquis L. Cummings 917 Bracero Road Encinitas, CA 92024	D. Is delivery address different from item 1? ☐ Yes If YES, enter delivery address below: ☐ No 3. Service Type ☒ Certified Mail ☐ Express Mail ☐ Registered ☐ Return Receipt for Merchandise ☐ Insured Mail ☐ C.O.D. 4. Restricted Delivery? (*Extra Fee*) ☐ Yes
2. Article Number (*Transfer from service label*)	7005 1820 0006 3811 8587

PS Form 3811, February 2004 Domestic Return Receipt 102595-02-M-1540

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Lin Zhi *et al.*
Serial No. : 10/080,503
Conf. No. : 8671
Filed : February 22, 2002
Art Unit : 1623
Examiner : Lawrence E. Crane, Ph.D.
Customer No.: 20985
Title : **TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS**

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

ATTACHMENT TO THE PETITION UNDER 37 C.F.R. §1.47

EXHIBIT 10 – copy of the substitute DECLARATION executed by joint inventors Robert I. Higuchi, Lin Zhi, Donald S. Karanewsky, Neelakandha S. Mani, Jyun-Hung Chen, Mark E. Adams and Charlotte L.F. Deckhut.

DECLARATION FOR PATENT APPLICATION

As below-named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled

TRICYCLIC QUINOLINONE AND TRICYCLIC QUINOLINE ANDROGEN RECEPTOR MODULATOR COMPOUNDS AND METHODS

the specification of which:

( ) is attached hereto.
(X) was filed by an authorized person on my behalf on February 22, 2002 as Application Serial No. 10/080,503
(X) was amended on January 31, 2005, November 3, 2005, May 19, 2006, and by Examiner's amendment of July 11, 2006.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

We hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate listed below and so identified, or §365(a) of any PCT international application that designated at least one country other than the United States of America, listed below, and we have also identified below any foreign application for patent or inventor's certificate or PCT international application on this invention filed by us or by legal representatives or assigns and having a filing date before that of the application on which priority is claimed.

Number	Country	Day/Month/Year Filed	Priority Claimed (Yes or No)
N/A			

We hereby claim benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application Serial No.	Filing Date
60/271,115	February 23, 2001

We hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
N/A		

PCT Application No.	Filing Date	Status
N/A		

We hereby declare that all statements made therein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Full name of joint inventor: Robert I. Higuchi

Inventor's signature: Robert I. Higuchi

Date: 11/3/06

Residence: 434 Marview Drive
San Diego, CA 92075

Citizenship: U.S.A

Full name of joint inventor: Lin Zhi

Inventor's signature: [signature]

Date: 10/26/06

Residence: 3988 Via Cangrejo
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: Donald S. Karanewsky

Date: 01 Nov 2006

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ____________________

Date: ____________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ____________________

Date: ____________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ____________________

Date: ____________________

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Donald S. Karanewsky

Inventor's signature: ________________

Date: ________________

Residence: 1797 Continental Lane
Escondido, CA 92029

Citizenship: U.S.A.

Full name of joint inventor: Anthony W. Thompson

Inventor's signature: ________________

Date: ________________

Residence: 4179 Third Avenue, Apt. 211
San Diego, CA 92103

Citizenship: U.S.A.

Full name of joint inventor: Thomas R. Caferro

Inventor's signature: ________________

Date: ________________

Residence: 101 Thoraton Green Pl.
Holly Springs, NC 27540

Citizenship: U.S.A.

Full name of joint inventor: Neelakandha S. Mani

Inventor's signature: ________________

Date: 11/1/06

Residence: 13109 Russet Leaf Lane
San Diego, CA 92129

Citizenship: India

Full name of joint inventor: Jyun-Hung Chen

Inventor's signature: Jyun-Hung Chen

Date: Oct. 26, 2006

Residence: 7614 Palmilla Drive, #58
San Diego, CA 92122

Citizenship: Taiwan

Full name of joint inventor: Marquis L. Cummings

Inventor's signature:

Date:

Residence: 917 Bracero Road
Encinitas, CA 92024

Citizenship: U.S.A.

Full name of joint inventor: James P. Edwards

Inventor's signature:

Date:

Residence: 8723 Hesby Court
San Diego, CA 92129

Citizenship: U.S.A.

Full name of joint inventor: Mark E. Adams

Inventor's signature: Mark Adams

Date: 11/28/06

Residence: 12638 Carmel Country Road, #130
San Diego, CA 92130

Citizenship: U.S.A.

Full name of joint inventor: Charlotte L.F. Deckhut

Inventor's signature: ______________________

Date: 11/28/06

Residence: 3105 Kalmia Street
San Diego, CA 92104

Citizenship: U.S.A.

IFW

Attorney's Docket No.: 18202-018001 / 1082

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

Dear Sir:

Transmitted herewith are a Substitute Petition under 37 C.F.R. §1.47 for acceptance of a substitute DECLARATION for an application for patent when a joint inventor cannot be reached or located or refuses to sign, with attachments and a return postcard in connection with the above-captioned patent application. If a Petition for extension of time is needed, this paper is to be considered such Petition.

☒ The Commissioner is hereby authorized to charge any fee, including that submitted herewith if the attached check(s) is in the wrong amount or otherwise improper or missing, that may be due in connection with this and the attached papers, or with this application during its entire pendency to or to credit any overpayment too Deposit Account No. 06-1050. A duplicate of this sheet is enclosed.

Respectfully submitted,
Fish & Richardson P.C.

Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 18202-018001 / 1082
Address all correspondence to:
Stephanie Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com

CERTIFICATE OF MAILING BY "EXPRESS MAIL"
"Express Mail" Mailing Label Number EV 740126578 US
Date of Deposit: **December 22, 2006**
I hereby certify that this paper is being deposited with the United States Postal "Express Mail Post Office to Addressee" Service under 37 CFR §1.10 on the date indicated above and is addressed to: Mail Stop Petition, Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA, 22313-1450.

Frank J. Miskiel